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(54) **FORMULATIONS CONTAINING HYALURONIC ACID**

HYALURONSÄURE ENTHALTENDE FORMULIERUNGEN

COMPOSITIONS CONTENANT DE L'ACIDE HYALURONIQUE

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Description

FIELD OF INVENTION

[0001] This invention relates to the combined use of a therapeutic agent and a determined form of hyaluronic acid, for the manufacture of a medicament for the topical treatment of disease and conditions of the skin and exposed tissue. In some embodiments this invention finds application to the treatment of a disease or condition of the skin and exposed tissue including basal cell carcinoma, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies and tumours in the skin, genital warts (condyloma acuminata), cervical cancer, HPV (Human Papilloma Virus) including HPV (Human Papilloma Virus) on the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet, actinic keratoses lesions, "liver" spots, fungal lesions, and other such types of lesions, and hair loss on the head of a pregnant women.

[0002] This invention also relates to compositions and formulations suitable for use in such treatments, the use of such formulations in such treatments, methods of such treatment, and the delivery of drugs for such treatments.

BACKGROUND OF THE INVENTION

[0003] Basal cell carcinoma is presently treated by surgery. Each lesion, together with all surrounding and underlying tissue (dermis, epidermis, and subdermis), is cut out. In some instances, surgery, while necessary for the patient's welfare, puts the patient at risk in some other respect (for example, the removal of a lesion on a patient's temple (resection) may jeopardize the patient's health). Squamous cell tumours are also treated the same way as are other forms of cancer in the skin and exposed tissue. Furthermore, other conditions and diseases of the skin and exposed tissue are treated in the same way or in ways that cause discomfort to the patient, for example melanoma, genital warts, cervical cancer, HPV (Human Papilloma Virus).

[0004] Actinic keratoses lesion is dealt with similarly. Liquid nitrogen is also used to remove the lesion.

[0005] These diseases and conditions are usually found in the epidermis (at least for the most part, extending into the dermis and upwards through the Stratum Corneum).

[0006] Hyaluronic acid is a naturally occurring glycosaminoglycan. Its molecular weight may vary from 50,000 daltons upwards, and it forms highly viscous solutions. As regards the actual molecular weight of hyaluronic acid in natural biological contexts, this is still a matter of much uncertainty; when the molecular weight of hyaluronic acid is to be determined, different values are obtained depending on the assay method employed, and on the source, the isolation method etc. The acid occurs in animal tissue, e.g. spinal fluid, ocular fluid, synovial fluid, cockscombs, skin, and also in some streptococci. Various grades of hyaluronic acid have been obtained. A preparation with an allegedly high degree of purity and alleged to be entirely free from side effects, is a non-inflammatory form described in U.S. Patent No. 4,141,973; this preparation is said to have a molecular weight exceeding 750,000 dalton, preferably exceeding 1,200,000 dalton and is suggested for therapeutic use in various articular conditions. Applicants believe that hyaluronic acid claimed in this patent is sold under the trade mark Healon.

[0007] United States Patent 4,801,619 relates to hyaluronic acid,having a molecular weight of about 3 X 10^6 dalton or more, administered intra-articularly which is prone to decrease the proteoglycan content of synovial fluid to almost normal levels. According to this patent, this indicates a a positive effect on the proteoglycan metabolism of a joint, according to the patent, this is applicable both to inflammatory conditions and to degeneration caused by treatment with symptomatics, such as corticosteroid preparations. It is thus clear that a sufficiently high molecular weight of the hyaluronic acid is alleged to counteract side effects that might be caused by corticosteroids or other symptomatics producing similar effects. When corticosteroids are applied, the amount of hyaluronic acid in the synovial cavity will, according to the patent, increase substantially and, according to the inventors, their hyaluronic acid preparations have a very positive effect on such clinical symptoms as pain, swelling, and lameness.

[0008] The patent states that the objectives of the invention are attained by intra-articular administration (injection) of an effective amount of hyaluronic acid with a mean molecular weight exceeding 3 X 10^6 dalton, preferably exceeding 4 X 10^6 dalton; usually the molecular weight will not exceed 7 X 10^6 dalton. The dosage of hyaluronic acid administered is stated to be preferably within the range of 5mg-80mg. The amount of solution given at each administration is generally less than 60 ml, e.g. less than 20 ml. of an aqueous solution of the acid or its salt. It is convenient to administer the acid dissolved in water (<2% w/w, buffered to physiological pH), for instance in the form of a water-soluble sodium salt. The exact amount will depend on the particular joint to be treated.

[0009] The Merck Index Specifies that Hyaluronic Acid has a molecular Weight within the range pf 50,000 to 8 X 10^6 depending on source, methods of preparation, and methods of determination. The Merck Publication teaches hyaluronic acid as a surgical aid (ophthalmological).

[0010] United States Patent 4,808,576 purports to teach that hyaluronic acid, an agent well known for reducing the sequelae of trauma in mammalian joint tissue when injected directly into the traumatized joint tissue, will be carried to

such traumatized tissue by the mammal's natural processes if applied at a site remote from the traumatized tissue. Thus, hyaluronic acid in any therapeutically acceptable form can, according to the Patent, be administered by the typical remote routes including intravenous, intramuscular, subcutaneous, and topical.

[0011] This, the patent alleges, makes the utilization of hyaluronic acid much more convenient and attractive. For instance, the treatment of arthritis in horse or human joints with hyaluronic acid, according to the patent, no longer requires more difficult intra-articular injections.

[0012] United States Patent 4,725,585 relates to a method of enhancing or regulating the host defence of a mammal by administering to a mammal a therapeutically effective amount of hyaluronic acid.

[0013] At column 1, lines 43 - 46, the patent provides that the invention was based on the unexpected discovery that administration of hyaluronic acid to mammals results in a considerable increase in the defence.

[0014] The hyaluronic acid employed in the patent was Healon (t.m) provided by Pharmacia AB, Uppsala, Swedon (Pharmacia AB is also entitled to the benefit of United States Patent 4,141,973). The patent provides at column 4, line 19 that because a patient's infections had been hard to treat, instead of just hyaluronic acid being administered to the patient to increase the patient's defence, the patient was given hyaluronic acid and an antibiotic. While one reading the patent may conclude that the antibiotic was given in combination with hyaluronic acid, in fact because the hyaluronic acid was administered subcutaneously and because the patient was a heart patient, one skilled in the art would understand that any antibiotic administered, while possibly administered simultaneously with the administration of the hyaluronic acid, was definitely administered separately intravenously (probably) or intramuscularly (less probably). Thus, the hyaluronic acid administered, according to the teachings of this patent, was administered in order to prevent possible development of infections (increase the host 's defence) and not for any other reason.

[0015] United States Patent 4,636,524 discloses cross-linked gels of hyaluronic acid, alone and mixed with other hydrophilic polymers and containing various substances or covalently bonded low molecular weight substances and processes for preparing them. These products are alleged to 30 be useful in numerous applications including cosmetic formulations and as drug delivery systems.

[0016] The patent further states that as hyaluronic acid is known to be a biologically tolerable polymer in the sense that it does not cause any immune or other kind of response when introduced into a human body. the cross-linked hyaluronic acid gels can be used for various medical applications. The cross-linked gels modified with other polymers or low molecular weight substances, it is alleged. can be used as drug delivery devices. For example, the inventors are alleged to have found that heparin introduced in a cross-linked hyaluronic acid gel retained its thrombogenic activity.

[0017] The inventors also allege that they have also found that cross-linked gels of hyaluronic acid can slow down the release of a low molecular weight substance dispersed therein but not covalently attached to the gel macromolecular matrix.

[0018] WO-A-91/04058 discloses combinations and formulations for the treatment of a disease or condition, comprising a therapeutic agent and a form of hyaluronic acid in an amount sufficient to facilitate the agent's penetration through the tissue at the site to be treated through the cell membranes into the individual cells to be treated. The amount of the form of hyaluronic acid in the combination of WO-A-91/04058 must be such as to provide doses exceeding 10mg. The topical administration of the formulations disclosed in the patent application is also mentioned and exemplified throughout the disclosure.

[0019] EP-A-019771. corresponding to US patent 4736024, reports to teach new medicaments for topical use containing:

(i) an active pharmacological substance or a mixture of pharmacological substances, either active or suitable for topical administration and

(ii) a topical vehicle which comprises hyaluronic acid or a molecular fraction of hyaluronic acid or a salt of same with an alkaline metal, an alkaline earth metal, magnesium, aluminium, ammonium, or a pharmacological substance optionally together with additional conventional excipients pharmaceutical preparations for topical use.

[0020] Applicants are also aware of published Japanese Patent Document 61000017, dated 86/01/06, whose English abstract of disclosure states that the Japanese Patent Document relates to the use of hyaluronic acid or cross-linked hyaunonic acid or their salts as the active ingredient for inhibiting carcinoma metastasis.

[0021] According to the purported abstract of the patent, more that 1.0% of hyaluronic acid is dissolved in alkaline aq. soln, and pref. more than 50% of H_2O sol org. solvent. eg. alcohol, acetone, dioxane, against total soln. is added. Preferably the pH is 12-14. Then a multifunctional epoxy cpd. added and reacted at 10-60 deg. C, pref. at 20-40- deg. C 24 hrs. Cross-linking ratio of crosslinked hyaluronic 1 or its salt is regulated by changing mol ratio of hyaluronic acid or its salt and multifunctional epoxy cpd.. Pref . hyaluronic acid used has intrinsic viscosity 0.2-30,m.w. 4000-2000000. The hyaluronic acid is allegedly used in several dosage forms. The clinical dose for an adult is alleged to be normally, as hyaluronic acid or cross-linked hyaluronic acid, 25mg-5 g/day (p.o.) and 10 mg-2.5 g/l dose (inj). The abstract alleges that the advantage is that the hyaluronic acid has no side effects as may other anti-cancer drugs and has an analgesic

and a tissue restoration effect.

[0022] European Patent Application 0295092 purports to teach a vehicle together with fragments of hyaluronic acid for delivering of the fragments of hyaluronic acid into the skin to reach the dermal layer of the skin to increase the development of blood vessels for stimulating hair growth or regrowth. The preferred fragments of hyaluronic acid are polysaccharides containing from 7 to 25 monosaccharide units. The patent provides that it is apparent that the larger the fragments of hyaluronic acid, the greater the difficulty there is in delivering the fragments to the dermal layer of the skin, unless there is also present in the composition a means for enhancing the activity of said fragments.

[0023] The combination may thus include a means for enhancing the activity of the fragments of hyaluronic acid, especially to improve their penetration through the skin following topical application. Some activity enhancers, it is alleged, also function as vehicles for the fragments of the hyaluronic acid.

[0024] Some activity enhancers are also alleged to possess the ability to stimulate or increase hair growth. Minoxidil is asserted among others to be such an activity enhancer. Thus both the fragments of hyaluronic acid and minoxidil are alleged to stimulate hair growth both delivered by a vehicle.

[0025] European Patent Application 0179442 asserts that where free radicals are formed in considerable quantities, hyaluronic acid is broken down or degraded before the hyaluronic acid has given the desired effect.

[0026] Canadian Letters Patent 1,240,929 teaches the combination of chondroitin sulfate compound and a hyaluronate to protect both human and animal cell layers and tissue subject to exposure to trauma.

[0027] European Patent Application 0208623 purports to each hyaluronic acid as "une augmentation de l'activité de certaines proteases". It also purports to teach the use of hyaluronic acid for treating connective tissue diseases, including malignant tumours and cardiovascular disorders.

[0028] European Patent Application 270317 purports to teach the combination of an antiviral agent lacking inhibitory action and a compound [for example. hyaluronic acid] possessing cell fusion inhibitory activity and/or virus-adsorption inhibitory activity for treating disease carried by a virus.

[0029] United States Patent 4,840,941 purports to teach the use of an effective amount of hyaluronic acid as the active agent for the treatment of retroviruses in association with a pharmaceutically acceptable carrier, diluent, or excipient.

[0030] United States Patent 4,851,521 and European Patent Application 0265116 both describe hyaluronic acid fractions, the making thereof and cross-linked esters of hyaluronic. United States Patent 4,851,521 describes esters of hyaluronic acid incorporated into pharmaceutical preparations as the active ingredient and as vehicles for ophthamological medicines for topical use (See column 11. lines 35 to 42; and column 12, lines 62 to column 13, line 3) and in suppositories for a systemic effect due to the effect of transcutaneous absorption, such as in suppositories.

[0031] The patent provides at column 13, lines 5 to 31.

[0032] "The vehicling action of the hyaluronic esters also applies to associated medicaments of the type mentioned above in which the active substance acts not only topically or by nasal or rectal absorption. for example by nasal sprays or preparations for inhalation for the oral cavity or the pharynx, but also by oral or parenteral route. for example by intramuscular, subcutaneous or intravenous route, as it favors absorption of the drug into the application site. The new medicaments can therefore be applied, apart from in the fields already mentioned, in practically all sectors of medicine, such as internal medicine. for example in pathologies of the cardiovascular system, in infections of the respiratory system. the digestive system, the renal system, in diseases of an endocrinological nature, in oncology, in psychiatry etc., and may also be classified therefore from the point of view of their specific action, being perhaps anesthetics, analgesics, anti-inflammatories, wound healers, antimicrobics, adrenergic agonists and antagonists, cytostatics, antirheumatics, antihypertensives, diuretics, sexual hormones, immunostimulants and immunosuppressants, for example, one of the drugs having the activity already described for the therapeutically active alcohols to be used as esterifying component according to the present invention, or for the therapeutically active bases used for the salification of the free carboxylic groups."

[0033] There have been extensive studies to determine the defect in immune function that allows a tumour cell to develop. It was postulated initially by Jerne, and subsequently by Burnett. that the immune system's major role was that of immunological surveillance to destroy abnormal cells. The concept of surveillance, while somewhat simplistic, remains an accepted concept for the elaborate mechanism of immune recognition and function that is present in the higher species - mammals.

[0034] It has then been postulated that tumours develop because of local or generalized immune suppression. However, as pointed out by Moller, if general immune suppression occurs, it is only certain types of neoplastic disorders that develop, mainly those of the lympho-reticular system. This observation is generally correct and represents a major challenge to the immune surveillance theory unless a specific reason can be shown as to why the individual cancer cell can develop plus individually evade the immune system.

[0035] It was demonstrated experimentally in 1974 that defects of macrophage function may exist in neoplastic disease.

[0036] The initial experiments found suppressor cells to be part of the immune system; these were either of the T-

cell type of the macrophage cell system. There was presence demonstrated in neoplasia, chronic bacterial infection, recovery from massive injury and chronic fungal infection.

[0037] There has been repeated demonstration in experimental animals that the macrophage cell function is altered in neoplastic disease. The macrophages in the animal's systems appeared "blocked" in their function. Generally when removed from the *in vivo* situation, washed in saline and cultured, they perform normally. This block has been shown to be related to the excessive production of prostaglandin by neoplastic tissue or by the macrophage itself. Similarly, the N.K. cells (which are said to be primitive or immature macrophages and which may be involved in cancer defence) are also blocked.

[0038] In the basic research efforts in the latter '70s and the early '80's, there existed considerable confusion as to what role immunotherapy should take in cancer. Activation or "hyping" of macrophages was thought to be important. However, in an examination by Romans and Falk of peritoneal macrophages obtained from patients with neoplastic disease, there was definite evidence that these macrophages were already activated yet were co-existing with cancer cells and not causing their destruction.

[0039] It has recently been shown by several independent investigators that the malfunction of macrophages or the putitive block is due to excessive prostaglandin and that this can be altered in tissue culture by corticosteroids, ASA, and the non-steroidal anti-inflammatory drugs, i.e. indomethacin and naproxen (Naprosyn™) . Again, it was repeatedly demonstrated that in animal tumours these substances could alter the response to neoplastic cells and that various combinations of these substances employed with immune enhancing agents could produce very credible success in eliminating experimental tumours. Lala and co-workers combined Indomethacin therapy with Interleukin 2 and showed that this could effect a cure with experiment neoplasm.

[0040] There were continued problems with the use of any of these agents in the actual human *in vivo* experience. All of the non-steroidal anti-inflammatory agents (NSAID) produced major toxicity in terms of gastro-intestinal, neurological, and other areas. Thus, the basis of the present approach is that, under general circumstances, with the use of these agents in human disease in sufficient amounts, the drug will penetrate to any pathological tissue to alter therapeutically local prostaglandin production. While intravenous preparations of Indomethacin (and now of other agents) exist, using these drugs alone produces prohibitive side effects in human subjects. Therefore, only insufficient amounts can be brought into the body to effect more than occasional responses in neoplasm.

[0041] However, the majority of the evidence is present to indicate and therefore, it can be postulated that the basis for neoplastic development and how the initial cell "sneaks by" the immune surveillance mechanism, relates to its production of prostaglandin. One need postulate only one mutation to alter the amount of prostaglandin synthesis produced by cells when they become "malignant" to establish a mechanism of blocking out the initial cell in any immune reaction, i.e. the macrophage. It therefore became essential to develop a combination of NSAIDs for clinical use to produce a major improvement in response in neoplastic disease and other conditions where excessive prostaglandin synthesis represents the basis of the pathogenesis of this disease state, i.e. arthritis and various others of the so-called connective tissue inflammatory disorders and/or auto-aggressive diseases.

[0042] See also:

1. Modulation of Immunity in Cancer Patients by Prostaglandin Antagonists, Immunity to Cancer II, Alan R. Liss, Inc.; and
2. Goodwin, J.S., (1981) Prostaglandin E and Cancer Growth Potential for Immunotherapy with Prostaglandin Synthesis Inhibitors, Augmentive Agents in Cancer Therapy, Raven Press, New York.

[0043] United States Patent 4,711,780 teaches a pharmaceutical composition comprising Vitamin C, a zinc salt, and a sulfur amino acid for treating surface epithelium for epithelium regeneration. Hyaluronic acid may be added for applications in the reproductive tract to block the passage of toxins into the blood system.

[0044] U.S. Patent 4,937,254 (Ethicon) teaches combinations of hyaluronic acid and salts thereof with NSAIDS for the prevention of adhesions after surgery.

[0045] Because of the side effects of the use of non-steroidal anti-inflammatory drugs (major toxicity in terms of gastro-intestinal, neurological, and other areas),use thereof should also be restricted (if possible) to the area of use without delivery to other areas which are not in need of treatment. Thus, if useful amounts of the non-steroidal anti-inflammatory drugs or for that matter any drugs could be delivered to a site in need thereof without carriage of substantial amounts away from the site to be treated, thereby accumulating an amount of the drug at the site to be treated for a prolonged period of time, then the use of the drug for example a non-steroidal anti-inflammatory drug at a site may have many other useful applications.

SUMMARY OF THE INVENTION

[0046] Applicants have now developed compositions, (combinations and formulations) which are topically applied

to the skin and/or exposed tissue of a human and which are quickly transported in dosage amounts percutaneously (intracutaneously) at a site in need of treatment, (site of pathology and/or trauma) best targeting the epidermis and subsequently remaining (accumulating) at the site for a prolonged period of time. The compositions subsequently clear through the lymphatics thereby bringing dosage amounts of the compositions to the lymphatics for the treatment of disease and conditions in the lymphatics.

[0047] These compositions, (combinations and formulations) employ, combine, or incorporate (as the case may be) a plurality of effective non-toxic dosage amounts, each dosage amount comprising an effective non-toxic dosage amount of a drug for example a drug which inhibits prostaglandin synthesis for example an NSAID and an effective non-toxic dosage amount of a form of hyaluronic acid (preferably hyaluronic acid or salt thereof) for the transport of the drug to the site of the pathology and/or trauma. Suitable dosage amounts of the composition may be removed from a container (for example a tube or jar) and administered (for example applied).

[0048] The invention provides the use of:

(1) a medicinal and/or therapeutic agent in a therapeutically effective amount to treat a disease or condition of the skin and/or exposed tissue and;
(2) a form of hyaluronic acid selected from hyaluronic acid and salts thereof having a molecular weight ranging from 150,000 daltons to less than 750,000 daltons for the manufacture of a pharmaceutical composition for the topical treatment of said disease or condition of the skin and/or exposed tissue.

characterized in that said composition is suitable to be applied in a dosage amount in which component (2) exceeds 5 mg/cm^2 of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition to be treated in the skin or exposed tissue, where the dosage amount of the composition accumulates (in the epidermis) for a prolonged period before passage therefrom, and wherein component (2) is 1 to 3% by weight of the composition.

[0049] According to the invention there is also provided a composition comprising in a form suitable for administration to the skin and/or exposed tissue of a human, an effective amount of a non-steroidal anti-inflammatory agent (NSAID), being between 1% and 5% of the composition by weight and an amount of hyaluronic acid and/or salts thereof having a molecular weight greater than 150,000 daltons and less than 750,000 daltons and being between 1% and 3% by weight of the composition. a preservative and a solubilizer if required and water.

[0050] According to the invention there is also provided the further uses, compositions and dosage amounts as recited in the claims.

[0051] Thus according to one aspect of the invention these pharmaceutical compositions (combinations and formulations) comprise a plurality of effective non-toxic dosage amounts for administration to the skin and/or exposed tissue of a human in need of treatment, each such dosage amount comprising a therapeutically effective non-toxic (to the patient) dosage amount of a drug to treat a disease and/or condition for example a drug which inhibits prostaglandin synthesis, preferably being a non-steroidal anti-inflammatory drug (NSAID), for example, diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac (sold under the trademark Toradol™) and an effective non-toxic dosage amount (for example in excess of 5 mg per cm^2 (square centimeter) of skin or exposed tissue to which the dosage amount of the composition is to be applied) of hyaluronic acid and/or salts thereof (for example the sodium salt) and/or homologues. analogues, derivatives, complexes, esters, fragments, and/or sub units of hyaluronic acid (preferably hyaluronic acid and/or salts thereof) to transport (to facilate or cause the transport of) the drug to the site of the pathology and/or trauma of the disease or condition. These compositions may be applied topically to treat diseases and conditions of the skin and/or exposed tissue at the site of the trauma and/or pathology. (for example, basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis), squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies and/or tumours in the skin, genital warts (condyloma acuminata), cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women). The results of the treatment with suitable dosage amounts taken from these compositions (combinations and formulations) have been in some instances quite dramatic - difficult situations have been successfully treated and resolved.

[0052] Furthermore, application of the dosage amounts of the compositions, combinations and formulations are, systemic independent (there is a lack of a blood level of the drug for example NSAID), are quick to penetrate into the skin to the site of the trauma and/or pathology because the effective dosage amount of the form of hyaluronic acid transports (facilitates or causes the transport of) the drug (for example NSAID) particularly to the epidermis where the composition, combination or formulation accumulates and remains for prolonged periods. The compositions subsequently clear through the lymphatics and are available for the treatment of disease and conditions of the lymphatics.

[0053] In this regard effective amounts of the form of hyaluronic acid exceeds in the order of about 5 mg per square

cm. (cm^2) of the area of for example the skin and/or exposed tissue to which the dosage amounts of the composition is to be applied.

[0054] Thus, according to another aspect of the invention, Applicants have provided topically applicable percutaneous (intracutaneous) penetrating (best targeting the epidermis) systemic independent acting (not acting essentially through the blood) pharmaceutical compositions (combinations and formulations) comprising a plurality of dosage amounts each comprising, together with pharmaceutical excipients suitable for topical application, a therapeutically effective (to treat and to assist to resolve diseases and conditions of the skin and exposed tissue (for example basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis), squamous cell tumours, metastatic cancer of the breast to the skin, malignancies and/or tumours in the skin primary and metastatic melanoma in the skin, genital warts (condyloma acuminata), cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix. psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women), non-toxic (to the patient) dosage amount of a drug for example which inhibits prostaglandin synthesis, preferably a non-steroidal anti-inflammatory drug (NSAID), for example, diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac (sold under the trademark Toradol™) and an effective non-toxic amount of hyaluronic acid and/or salts thereof (for example, the sodium salt) and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid (preferably hyaluronic acid and salts thereof) to transport (facilitate or cause the transport of) the drug (for example NSAID's) rapidly to the site in the skin (for example epidermis) and/or exposed tissue of the disease or condition into the tissue to remain there for a prolonged period of time to assist to treat and assist to resolve the disease or condition for example by blocking prostaglandin synthesis.

[0055] Effective dosage amounts of the form of hyaluronic acid to facilitate or cause the transport of the drug into the skin and/or exposed tissue by the form of hyaluronic acid exceeds about 5 mg. - 10 mg. in the dosage amount administered (applied and rubbed in) for each 1 cm^2 of skin and/or exposed tissue area of the disease or condition (for example basal cell carcinoma) to which the dosage amount is applied. The dosage amount applicable will depend upon the surface area of the skin and/or exposed tissue in which the condition or disease exists. Thus if the disease or condition occupies about .5 cm^2, in excess of about 2½ mg of the form of hyaluronic acid would be used (applied and rubbed in). In the same way if the area is 2 cm^2, the amount of the form of hyaluronic acid preferably exceeds about 10-20 mg of the dosage amount of the formulation or composition applied. Preferred forms of the hyaluronic acid (for example hyaluronic acid and the sodium salt thereof) have molecular weights less than about 750,000 daltons (for example about 150,000 to about 225,000 daltons) to transport the medicine in the skin and/or exposed tissue. While higher molecular weights of the hyaluronic acid and forms thereof may be used to penetrate the skin and/or exposed tissue and transport the medicines or drugs, where the molecular weight of the hyaluronic acid chosen for use is very large, it is preferred that the form of hyaluronic acid is autocleaved, to break down the hyaluronic acid to fragments of lesser molecular weight or if feasible diluted to permit administration and ensure no coagulation on or in the skin. Where the molecular weight of the form of hyaluronic acid being employed is large, the concentration of the form of the hyaluronic acid in the composition may for example be reduced (for example to less than about 3%) dependent on the molecular weight.

[0056] The blockage of prostaglandin synthesis by the transported drug (for example NSAIDS) then unblocks the macrophages and permits the macrophages of the patient proximate the lesion (for example, the basal cell carcinoma) to destroy the lesion or condition. Treatment by dosage amounts of the composition (formulation and/or combination) eliminates the condition without recurrence, even where the lesion has recurred a number of times after unsuccessful treatments according to the prior art.

[0057] Other non-steroidal anti-inflammatory drugs (NSAIDS) may be used such as other propionic acid derivatives, Ibuprofen. acetylsalicylic acid, piroxicam and flunixin.

[0058] When dosage amounts of such compositions, combinations and formulations are applied to the site of the disease or condition for example the basal cell carcinoma of the patient suffering from the basal cell carcinoma, over a period of time (for example, for a period of 2-4 weeks 3 times daily) the basal cell carcinoma is completely resolved and disappears.

[0059] Thus according to another aspect of the invention there is provided a pharmaceutical composition from which dosage amounts may be taken for application to the skin and/or exposed tissue, the pharmaceutical composition comprising in a form for application to a human a plurality of dosage amounts. of medicine and/or therapeutic agent to treat a disease or condition in a human and a plurality of dosage amounts of hyaluronic acid and/or salts and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid such that when dosage amounts of the pharmaceutical composition are taken from the composition, the amount of the medicine and/or therapeutic agent comprises an effective non-toxic dosage amount of the medicine to treat the disease or condition in the skin and/or exposed tissue in a human and the amount of the form of hyaluronic acid in the dosage amount is present in an effective amount to transport (facilitate or cause the transport of) the medicine and/or therapeutic agent intradermally (percutaneously, intercutaneously, intracutaneously) into the skin (preferably to the epidermis and dermis) and/

or exposed tissue of a human to the site of a pathology and/or trauma. The effective amount of the form of hyaluronic acid has a molecular weight and concentration to transport the medicine (drug) and/or therapeutic agent to the site of trauma and/or pathology in the skin and/or exposed tissue. In this regard the preferred amount of the form of hyaluronic acid in each dosage amount exceeds 5 mg./cm^2 and preferably the molecular weight is less than about 750,000 daltons, (in one embodiment about 150,000 to about 225,000 daltons) in some embodiments with a concentration of between about 1 and 3%, preferably concentrations of between about 2 to about 3% by weight. Where forms of hyaluronic acid are used having greater molecular weights, they are preferably cleaved and/or diluted to smaller concentrations, to facilitate or cause the transport of the medicine and/or therapeutic agent.

[0060] According to another aspect of the invention there is provided a pharmaceutical composition (for example a gel or cream) from which dosage amounts may be taken and applied to the skin to treat a disease or condition in humans, for example as discussed above, the pharmaceutical composition comprising:

(1) a medicinal and/or therapeutic agent suitable for treating a disease or condition in the skin and/or exposed tissue in humans, for example a drug which inhibits prostaglandin synthesis (for example an NSAID); and
(2) hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and sub-units of hyaluronic acid, in a form suitable for administration to the skin and/or exposed tissue in humans; characterized in that an effective non-toxic dosage amount comprising components (1) and (2) taken and administered from said composition (i) is available in the skin and/or exposed tissue upon administration to treat said disease or condition in humans by penetration at the site to be treated to the site of trauma and/or pathology, and (ii) comprises an effective non-toxic dosage amount of component (2) effective to transport (facilitate or cause the transport of) component (1) immediately upon administration percutaneously into the skin (preferably the epidermis) to the site to be treated for example the site of trauma and/or pathology where it remains for a prolonged time, accumulating there and from which it is discharged via the lymphatic system.

[0061] Therefore according to another aspect of the invention a pharmaceutical composition is provided comprising:

(1) a medicinal and/or therapeutic agent which for example inhibits prostaglandin synthesis in a therapeutically effective amount to treat a disease or condition of the skin and/or exposed tissue;
and (2) hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and subunits of hyaluronic acid,

characterized in that said composition

(a) is in a dosage form (for example a gel or cream) which is suitable for administration to the skin and/or exposed tissue;
and (b) is in such an amount and in such form that (i) component (1) is in an effective dosage amount to treat said disease or condition by penetration at the site of the skin and/or exposed tissue to be treated for example the basal cell carinoma and other lesions; and (ii) component (2) is immediately available to transport (facilitate or cause the transport of) component (1) to the site of trauma and/or pathology to be treated, percutaneously into the skin (or exposed tissue) where the composition resides and accumulates for a prolonged period, and which component (2) is in an effective non-toxic dosage amount to transport (facilitate or cause the transport of) component (1) upon administration, percutaneously into the skin or exposed tissue to the site of the trauma and/or pathology. Preferably the form of hyaluronic acid in the composition comprises hyaluronic acid and/or salts thereof. An effective amount of the form of hyaluronic acid exceeds about 5-10 mg per square centimeter (cm^2) of skin and/or exposed tissue to which it is to be applied.

[0062] According to another aspect of the invention there is provided the use of:

(1) a medicinal and/or therapeutic agent for example which inhibits prostaglandin synthesis,
and
(2) hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and subunits of hyaluronic acid.

in the manufacture of a pharmaceutical composition for treating a disease or a condition (for example those discussed above) of the skin and/or exposed tissue in a therapy wherein dosage amounts taken from the composition each comprise:

(1) a therapeutically effective amount of said medicinal and/or therapeutic agent and

(2) a therapeutically effective amount of the hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments, and sub-units of hyaluronic acid, the pharmaceutical composition being characterized in that for each dosage amount taken from the pharmaceutical composition, the amount of component (2) is immediately available to transport component (1) percutaneously to the site of trauma and/or pathology for example into the epidermis where the composition accumulates and remains for a prolonged period, at the site of the skin or exposed tissue to be treated, and component (2) is in an effective non-toxic amount to transport (facilitate or cause the transport of) component (1) into the skin or exposed tissue (for example into the epidermis). Preferably component (2) is hyaluronic acid and/or salts thereof and preferably the dosage amount of component (2) in the amount of the composition taken from the composition (to be taken from the composition) and applied to the skin or exposed tissue is a dose amount greater than about 5-10 mg per cm^2 of skin and/or exposed tissue to which the dosage amount is to be applied.

[0063] The pharmaceutical composition will normally include pharmaceutically compatible excipients to provide a form for ease of administration to the skin and/or exposed tissue for transport into the epidermis. For example a suitable dosage amount of a gel may be squeezed from a tube as a ribbon of gel "X" cm long (which dosage amount (in the form of the ribbon "X" cm long) contains the effective non-toxic dosage amounts of the drug and form of hyaluronic acid. Or a dosage amount of cream packaged in a jar may be scooped from the jar by a measuring device or by "two fingers" in a suitable amount (for example in a spoon containing a premeasured volume or an amount about half the "length of the fingers"). Each of the dosage amounts selected comprises the effective amounts of drug (for example NSAID) and effective amount of the form of hyaluronic acid (for example hyaluronic acid and/or salts thereof). In this way the patient may "squeeze" or scoop" or "what have you" the appropriate dosage amount and apply (rub in) the dosage amount onto the skin and/or exposed tissue for transport into the epidermis.

[0064] One such formulation may comprise 3% (by weight) diclofenac in a 2½% (by weight) hyaluronic acid (sodium hyaluronate - molecular weight 661.600) gel formulation, with the excipients being glycerine (5%), benzyl alcohol (3%) (acting in part as a solubilizer and preservative), and sterile water (the balance) in a 50 g tube of the composition (a plurality of dosage amounts) whose tube O.D. (outer diameter) of the opening through which the gel formulation is discharged from the tube is 8 mm and whose I.D. (inner diameter) of the opening is 4 mm. Therefore a ribbon 2-3 cm in length, squeezed from a tube gives about 5 mg-7½ mg of hyaluronic acid for application to a skin or exposed tissue surface area of 1-1½cm^2 with an effective dosage amount of diclofenac. While greater amounts squeezed from the tube, may be applied, the application of substantial excessive dosage amounts to the skin and/or exposed tissue may saturate the skin or exposed tissue and thus the epidermis. (There is therefore no more room for the composition to pass between the cells and therefore further applications at that time will not provide additional benefit). Where pain relief is also required additional dosage amounts, for example in excess of about 10 mg of the hyaluronic acid taken from the same pharmaceutical composition applied per/cm^2 of surface area of the skin or exposed tissue may be required to be applied.

[0065] Another formulation may comprise 3% (by weight) diclofenac in a 2½ % (by weight) hyaluronic acid (sodium hyaluronate - molecular weight 879,000) gel formulation (also in a tube) with excipients being benzyl alcohol (1%) (a preservative), methoxypolyethylene glycol 350 (20% by weight) (a solubilizer), and sterile water (the balance).

[0066] While the above compositions, combinations and formulations are proposed, provided there is sufficient amounts of the form of the hyaluronic acid (for example, sodium hyaluronate) in the dosage amounts applied to the skin and/or exposed tissue to facilitate or cause the percutaneous (intracutaneous) transport of the drug for example which inhibits prostaglandin synthesis, preferably an NSAID (for example, diclofenac) to block prostaglandin synthesis, then the formulations may be of any suitable form, for example, a 1% lotion of hyaluronic acid with NSAID, or a cream or gel or any other suitable form.

[0067] Therefore according to another aspect of the invention, there is provided containers (for example tubes and jars) containing compositions comprising a plurality of dosage amounts of the drug and form of hyaluronic acid, each dosage amount comprising an effective non-toxic dosage amount of the drug and an effective non-toxic dosage amount of the form of hyaluronic acid (preferably sodium hyaluronate having molecular weight less than about 750,000 daltons) to transport the drug into the skin and/or exposed tissue. In some embodiments, means are provided to assist the removal from the container of an effective dosage amount of the composition in the container for use to apply to the skin or exposed tissue at the site of trauma and/or pathology to treat the disease and/or condition (for example mouth opening of a tube to control the amount discharged from the tube).

[0068] Furthermore, because there is little concern with respect to the toxicity or adverse effects of the use of, for example, the NSAIDs with the hyaluronic acid in the compositions of this invention the NSAID may be combined as needed (after solubilizing (if required) of the NSAID in a suitable solubilizer) with the form of the hyaluronic acid.

[0069] Delivery may be also accomplished by the same amount of the form of hyaluronic acid, of other drugs percutaneously (intercutaneously) to the skin and exposed tissue by application and rubbing in of an effective non-toxic dosage amount of the formulation or composition comprising an effective non-toxic dosage amount of the drug and an

effective non-toxic dosage amount of the form of hyaluronic acid for the transport of the drug percutaneously into the skin or exposed tissue to the epidermis where the dosage amount of the composition is accumulated and remains for a prolonged period of time before the form of hyaluronic acid is cleared through the lymphatics. In this regard the drug may be novantrone (an anti-cancer drug) for administration to a tumour or malignancy in the skin. The novantrone may comprise 10 mg in the dosage amount of the composition and the form of hyaluronic acid may be in excess of about 5 mg of sodium hyaluronic per cm^2 of the skin or exposed tissue (about 2.5% of the composition) for the percutaneous transport of the novantrone.

[0070] Applicants postulate that the hyaluronic acid and/or salts thereof and/or the homologues, analogues, derivatives, complexes, esters, fragments, and/or sub units of hyaluronic acid facilitate or cause the transport of the drug for example which blocks prostaglandin synthesis (preferably an NSAID) to the site of prostaglandin synthesis to block prostaglandin synthesis.

[0071] Applicants' compositions and dosage amounts of their compositions and the use of their compositions and dosage amounts of their compositions, at the same time, abate pain that the patient is experiencing at the paccinian nerve bundles (superficial nerve bundles) at the site of the trauma and/or pathology on/in the exposed tissue and/or skin.

[0072] Thus, according to another aspect of the invention, compositions are provided for use to relieve pain from which dosage amounts of the composition comprising dosage amounts of the NSAID and form of hyaluronic acid are taken.

[0073] By way of example and to illustrate the facilitation of the delivery or transport of a chemical to a site in a human, when ethyl alcohol is injected directly into a tumour and sonographic (ultrasound) assessment is made, it is not dispersed throughout the tumour. When the ethyl alcohol to be administered into a tumour is carried by hyaluronic acid and/or salts thereof, sonographic assessment of the tumour demonstrates the dispersion of the ethyl alcohol throughout the tumour.

[0074] While Applicants postulate that the hyaluronic acid facilitate or causes the transport and delivery, Applicants' invention may be used as described irrespective of the actual method of operation of the hyaluronic acid and/or salts thereof and/or the homologues, analogues, derivatives, complexes, esters, fragments and sub-units of hyaluronic acid.

[0075] The combination of hyaluronic acid and salts thereof and other forms with drugs for example that inhibit prostaglandin synthesis, for example NSAIDs, alters their distribution and performance in the skin and/or exposed tissue particularly the epidermis (the combinations and formulations being systemic independent), and produces an unusual targeting for underperfused skin and/or pathological tissue in the skin (site of trauma and/or pathology). The application may be made as required with the amount depending upon the condition of the skin or exposed tissue.

[0076] As a major amount of soluble indomethacin may be incorporated into the formulation, or composition, the indomethasin may be solubilized using n-methyl glucamine at a dilution of 5mg/ml of n-methyl glucamine (NMG). This substance is then passed through a 22 micron Milipore filter to produce sterility. This material is non-toxic at 16 fold the therapeutic dose in animals (with hyaluronic acid) and for this reason was considered appropriate to be used in human conditions. Thus, Indocid™ solubilized in NMG may be administered with hyaluronic acid topically for percutaneous penetration at, for example, varying doses. The solution of indomethacin and NMG may be mixed with, for example, "LifeCore™" hyaluronic acid in dosage amounts discussed above. This produces an appropriate mixture and can be administered safely.

[0077] When the NSAID, for example indomethacin (dissolved in n-methyl glucamine) or other NSAID, is applied topically in an effective dosage amount from a composition or formulation also including the effective dosage amount of the form of hyaluronic acid, no major toxic side effects occur, such as gastro-intestinal distress, neurological abnormalities, depression, etc., even at elevated amounts of indomethacin (if necessary). (This may be in part because of the clearing of the hyaluronic acid through the lymphatic system from the site). In addition, the responses that have been observed are dramatic when the drug for example NSAID (for example diclofenac) is combined with hyaluronic acid, demonstrating' clearly that the combination is now "targeting" to the site of pathology or trauma, or pathological tissue. Furthermore, patients using the formulations and combinations of drug (for example NSAID) - hyaluronic acid (sodium hyaluronate) (for example, diclofenac or indomethacin and hyaluronic acid), experience dramatic relief of pain immediately

[0078] Thus, Applicants believe that the use of the NSAID, for example with hyaluronic acid (sodium hyaluronate), deblocks the macrophages (and N.K. cells (Natural Killer Cells) thought to be immature macrophages) by preventing enzymatic production of prostaglandin which blocks macrophage (and N.K. cell) functioning. The hyaluronic acid (and salt and other forms) not only enhances the activity of the drug (NSAID) but also reduces any side effects and toxicity that is associated with the use of the prostaglandin synthesis inhibitors. When effective dosage amounts of compositions, formulations and combinations containing effective dosage amounts of the drugs for example, (NSAIDs (for example, diclofenac)) and effective dosage amounts of, for example, hyaluronic acid or the sodium salt thereof, are applied to for example the tumour lesion (for example basal cell carcinoma) or other condition (for example, actinic keratoses lesion) for a period of time (for example, 3 times daily for 2-4 weeks), the carcinoma and lesions, as the case may be, disappear.

[0079] Applicants also postulate that when the combination or formulation is applied to the disease or condition (for example, basal cell carcinoma or actinic keratoses), the hyaluronic acid passes between the cells (in the stratum corneum and epidermis to the dermis depending on amounts) to the areas of trauma and/or pathology deficient in hyaluronic acid (or forms thereof), transporting, taking, drawing, carrying or pulling the NSAID with it to the sites of prostaglandin synthesis, penetrating to inhibit prostaglandin synthesis until the space between the cells is saturated. The NSAID now being proximate the Paccinian nerve bundle (superficial nerve bundles at the end of the nerves) gives pain relief. The macrophages (which had been previously blocked) are unblocked and act to destroy the disease or condition for example basal cell carcinoma, actinic keratoses lesion, or other disease or lesion. Furthermore, the effective non-toxic dosage amount of the composition, combination or formulation, comprising the effective dosage amount of the form of hyaluronic acid and the effective dosage amount of NSAID passing through the stratum corneum to the epidermis and to the dermis (if a sufficient amount of the form of hyaluronic acid is present), passes into the skin, accumulating and staying longer in the skin at the site of the trauma and/or pathology. Therefore, after having had an immediate effect at the site of trauma and/or pathology (for example, relieving pain and acting on the basal cell carcinoma, actinic keratoses and other disease, condition or lesion), the NSAID-hyaluronic acid combination continues to accumulate at the site in need of treatment and thereafter clears through the lymphatic system.

[0080] Thus according to another aspect of Applicant's invention, Applicants' compositions, formulations and combinations quickly penetrate on application through the stratum corneum into the epidermis (to the dermis) by the form of hyaluronic acid transporting the NSAID, to the site of trauma and/or pathology where the amounts applied accumulate and remain for a prolonged time for treatment.

[0081] Fifteen (15) minutes after application of one of Applicants' formulations, about three times the amount of Applicants' formulation has penetrated into the skin (particularly the epidermis) than formulations and combinations not containing hyaluronic acid or effective dosage amounts of hyaluronic acid, but containing the same drug. Furthermore, the drug and hyaluronic acid accumulate and remain at the site in need of treatment for a longer period of time.

[0082] Thus according to another aspect of the invention, Applicants have provided compositions (formulations and combinations) (including pharmaceutical excipients suitable for topical application) from which effective non-toxic (to the patient) dosage amounts of a drug (for example an NSAID) to treat and to assist to resolve diseases and conditions of the skin and/or exposed tissue (for example basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis), squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies and/or tumours of the skin. genital warts, cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix. psoriasis (both plaque-type psoriasis and nail bed psoriasis) , corns on the feet and hair loss on the head of pregnant women), and effective non-toxic dosage amounts of hyaluronic acid and/or salts thereof (for example, the sodium salt) and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid (preferably hyaluronic acid and salts thereof) sufficient to transport (to facilitate or cause the transport of) the drug, for example NSAID, are taken for application, to a site in the skin (for example epidermis) or exposed tissue having a disease or condition for percutaneous transport into the skin and/or exposed tissue to accumulate and remain there for a prolonged period of time to for example block prostaglandin synthesis. Thus an effective dosage amount of the composition or formulation or combination penetrates quickly into the skin, for example by the hyaluronic acid transporting the NSAID or causing the NSAID to be transported for example to the epidermis of the skin, accumulates there and remains there for a prolonged period of time, thereby accumulating the drug and forms of hyaluronic acid in the skin (particularly the epidermis).

[0083] Thus according to another aspect of the invention a composition is provided which when administered to a human by preferably administration to the skin and/or exposed tissue of a human, unloads its contents into the lymphatic system. the composition comprising an effective non-toxic dosage amount of a drug (for example an NSAID or an anti-cancer drug (Novantrone) and an effective non-toxic amount of hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments and/or sub-units of hyaluronic acid (for example at least about 5-10 mg/cm^2 of skin or exposed tissue). Thus the composition is made up of a plurality of such dosage forms (for example a cream or lotion or gel).

[0084] According to another aspect of the invention, the composition may be for application to the skin or exposed tissue.

[0085] According to another aspect of the invention, a composition is provided from which effective dosage amounts may be taken and administered, each effective dosage amount of the composition comprising an effective non-toxic dosage amount of hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives. complexes, esters, fragments and/or sub-units for transporting a therapeutically effective non-toxic dosage amount of a medicine and/or therapeutic agent (for example an NSAID) in the composition into the skin and/or exposed tissue when applied thereto to an area of pathology and/or trauma then into the lymphatic system, the dosage amount being essentially systemic independent such that substantial amounts do not enter the blood system prior to clearing (passing) into the lymphatic system. Preferably the amount of the form of hyaluronic acid in each dosage amount administered is greater than

about 5-10 mg./cm^2 and the molecular weight is less than about 750,000 daltons.

[0086] We have compared the penetration and retention of one of our combinations (formulations) with a control and Voltarol Emulgel in the skin as follows:

(A) OUR FORMULATION				
1% DICLOFENAC IN 3.0% HA GEL 50g/tube				
EPDICLO1 LOT XPB 044		Quantity 1500ml		
FORMULA	Supplier	Lot	Amount	Percent
Sterile Water	Baxter	AW45F1	1397ml	--
Glycerin	Life	1043	45g(36ml)	3%
Benzyl Alcohol	Caledon	02517	22.5g(22ml)	1.5%
Liquid Wax DICDD	Brooks	191-175	45g	3%
Diclofenac Sodium	Prosintex	9113003	15g	1%
Sodium Hyaluronate Mol. Wt. 661,600	Skymart	HG-1103	45g	3%

PROCEDURE

[0087]

- Set up stirring apparatus using a 3 liter stainless steel beaker
- Add Water, Glycerin, Benzyl Alcohol and Liquid Wax DICDD, stir and mix for 10 minutes
- Add Diclofenac Sodium and stir for 30 minutes to dissolve
- Add Sodium Hyaluronate and stir for 90 minutes

FILLED

[0088] In a 50 ml aluminum collapsible tube, inside of tube lacquered with a phanolic resin, outside of tube white regular enamel coating; 9 mm white polypropylene screw on cap with pierce tip

	Gels	Batch No.s
(B)	Voltarol Emulgel	060400 10 93
(C)	1% Diclofenac Gel	XPBO49 (Control)

(C) CONTROL				
1% DICLOFFNAC IN CARAPOL GEL, 50g Jar				
LOT XPB 049		Quantity 100ml		
FORMULA	Supplier	Lot	Amount	Percent
Sterile Water	Baxter	AW45N5	93ml	--
Glycerin	BDH	2579	3g	3%
Benzyl Alcohol	BDH	23797	1.5g	1.5%
Liquid Wax DICDD	Brooks	L-1424	3g	3%
Diclofenac Sodium	Prosintex	9113003	1g	1%
Carbopol 934	A&C Chemicals	910304	1g	1%

PROCEDURE

[0089]

- Set up stirring apparatus using a 400ml stainless steel beaker
- Add Water, Glycerin, Benzyl Alcohol, Liquid Wax DICDD. and stir to mix thoroughly for 10 minutes
- Add Diclofenac Sodium and stir for 20 minutes to dissolve
- Very slowly add Carbopol 934, avoid getting lumps

Samples		
Cell	Sample	Quantity of gel applied (mg)
A	060400 10 93	192
B	060400 10 93	192
C	EPDICLO1*	192
D	EPDICLO1*	192
E	XPB049	192
F	XPB049	192

* - Our Formulation

Skin Type

[0090] One piece of skin (Female, 37 years, smoker, breast skin) was used for one sample from each batch. A second piece of skin (no further details available) was used for the second sample from each batch. The skin was stored deep frozen (<-20°C) until thawed for this experiment. Full thickness skin was used for this experiment.

Experimental Conditions

[0091] Skin permeation cells were prepared containing an exposed skin surface area of 9.6 cm^2 and a constantly stirred receptor fluid beneath the skin consisting of 135 ml of ethanol:phosphate buffered saline (25:75 v/v).

[0092] Each cell was allowed to equilibrate for 1 hour at 37°C after which the gel was spread evenly over the skin surface at a concentration of 20 mg/cm^2). See table above. The cell was then maintained at 37°C with an air temperature above the skin of 35°C.

[0093] 24 hours after application of the gel the experiment was stopped and a portion of the receptor fluid removed. The skin was removed from the cell and any gel remaining on the surface carefully wiped off with dry paper towel followed by paper towel moistened with water. The skin was cut with a scalpel to obtain thin top and thicker lower sections of skin.

[0094] This was done in order to obtain layers of skin which approximated the epidermal and dermal layers. Each skin section was weighed and the residual diclofenac extracted with 10ml of fresh receptor fluid using an ultra turrax homogeniser. The homogenates were centrifuged and a portion of the resultant supernatant solutions removed.

[0095] The receptor fluid and skin extracts from each cell were assayed for diclofenac content by using a validated reverse phase high performance liquid chromatography (HPLC) method.

Results

[0096]

Distribution of Diclofenac 24 hours after application of Diclofenac Gel							
Sample	Receptor	Top Skin portion			Bottom skin portion		
	µg	Skin Weight (g)	µg	µg/g	Skin Weight	µg	µg/g
(Voltarol Emugel)							
060400 10 93	447	0.1363	101	742	1.2449	217	174
060400 10 93	764	0.2445	141	577	1.2351	202	164
Mean	606			660			169
(Our Formulation)							
EPDICLO1	247	0.1535	133	867	1.4663	148	101
EPDICLO1	292	0.1647	145	879	1.0022	86	86
Mean	269			873			93
(Control)							
XPB049	184	0.1275	35	272	1.1324	58	51
XPB049	147	0.2068	82	396	1.0893	68	63
Mean	165			334			57

[0097] Thus having regard to the above and Figures 1', 2' and 3', it is clear that the sodium hyaluronate takes the diclofenac into the skin to the epidermis level (See Figure 1') more rapidly than the Voltarol Emugel or non-hyaluronic acid diclofenac containing control formulation, accumulates it there and retains it there longer. The other formulations permit the NSAID. diclofenac, to pass through the bottom skin portion (dermis) quicker, thereby clearing it from the epidermis and dermis, quicker. Furthermore, more of Applicants' formulation is in the epidermis and in the dermis even after 12 hours. With respect to Figure 1', the top of the graph should have the following heading "DICLOFENAC TOP SKIN PORTION", the left side of the graph should have the following side heading "DICLOFENAC (MICROGRAMS). (THOUSANDS)" and the bottom of the graph should have the following bottom heading "ELAPSED TIME (HOURS) □ 0604001093 + EPDICLO1 ◊ XP8049". With respect to Figure 2', the top of the graph should have the following heading "DICLOFENAC BOTTOM SKIN PORTION", the left side of the graph should have the following side heading "DICLOFENAC (MICROGRAMS)" and the bottom of the graph should have the following bottom heading "ELAPSED TIME (HOURS) □0604001093 + EPDICLO1 ◊ XP8049". With respect to Figure 3', the top of the graph should have the following heading "DICLOFENAC RECEPTOR SOLUTION", the left side of the graph should have the following side heading "DICLOFENAC (MICROGRAMS)" and the bottom of the graph should have the following bottom heading "ELAPSED TIME (HOURS) □060400 1093 + EPDICLO1 ◊ XP8049".

[0098] It is also clear that Applicants' formulations clear into the lymphatic system not through the blood system. Yet the prior art topical formulations have always tried "to drive" the formulations through the skin into the blood for treatment of the disease or condition in the area (i.e. systemic action).

[0099] Thus, our composition, formulation and combination, (and dosage amounts thereof) penetrate quickly and rapidly at the site of treatment through the upper skin into the epidermis, where the paccinian bundles are located and the NSAID and the form of hyaluronic acid are accumulated and are retained longer, where needed (for example for the treatment of basal cell carcinoma).

[0100] Further, the NSAIDs are retained in the area to be treated with the form of hyaluronic acid. In doing so, they preclude prostaglandin synthesis , in effect. deactivating the synthesis or inhibiting the synthesis, of prostaglandins, permitting the macrophages' scavenger cell activity to eliminate the tumour and lesion. Additionally, a rapid onset of pain relief (analgesic effect) is provided (depending on the amount of NSAID and form of hyaluronic acid) usually where in excess of about 10 mg of the form of hyaluronic acid (preferably hyaluronic acid and salts thereof) is administered per cm^2 of surface area comprises the dosage amount administered. However, there are no blood levels of the NSAID in the immediate area of treatment. The forms of hyaluronic acid are thus cleared via the lymphatic system. Then the lymphatics pass the forms of hyaluronic acid. Applicants believe. to the blood system. Thus, the NSAIDs and forms of

hyaluronic acid stay at the site to be treated for well in excess of 12 - 24 hours, a protracted stay.

[0101] Thus, over the period of treatment (for example, applications of effective non-toxic dosage amounts of compositions containing for example effective non-toxic dosage amounts of the NSAIDS and effective non-toxic dosage amounts of the sodium hyaluronate, 3 times a day for 2-4 weeks, transport the NSAIDS to to the epidermis to inhibit prostaglandin synthesis to enable the macrophages to "scavenge" the tumour cells and eliminate them. The end result is the successful treatment of the disease or condition at the site of trauma and/or pathology of the skin or exposed tissue, for example, the resolution of, the basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis), squamous cell tumours, metastatic cancer of the breast to the skin, malignancies and/or tumours in the skin, primary and metastatic melanoma in the skin, genital warts cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women, with complete disappearance of the disease or condition as the case may be, by topical therapy without resorting to surgery.

[0102] One of the formulations which we have employed successfully is a gel formulation comprising 3% diclofenac in 2.5% sodium hyaluronate formulated as follows:

Formulation 1 (3000 ml.)

[0103]

Formula	Supplier	(LOT)	Amount	Percent
Glycerine	Life	1043	150 g (119 ml)	5
Benzyl Alcohol	Caledon	02517	90 g (86 ml)	3
Diclofenac Sodium	Prosintex	9113003	90 grams	3
Sodium Hyaluronate (MW 661,660)	Skymark	HG1003	75 grams	2.5
Sterile water balance	Baxter	AW4455	2795 ml.	

Procedure

[0104]

- set up stirring apparatus using a 4 litre stainless steel beaker
- add water, Glycerine, and Benzyl Alcohol, stir to mix
- add Diclofenac Sodium and stir for 30 minutes
- then add the Sodium Hyaluronate and stir for 90 minutes
- initially, stir at a high torque but avoid splashing; as the gel thickens, stir at a lower torque.

[0105] The gel is then packaged in a tube or jar or other suitable container for use. Identification of suitable dosage amounts and how they are taken from the container may be provided with the container - for example squeeze "X" cm. of ribbon from the tube; fill spoon or spatula accompanying jar; (the spoon or spatula containing a predetermined dosage amount) then apply and rub into site of trauma and/or pathology (the dosage amount indicated will be such amount of the composition which comprises in excess of about 5 mg. of sodium hyaluronate per cm^2 (square centimeter) of skin or exposed tissue to which the dosage amount is to be applied. The amount of Diclofenac Sodium was determined in the same manner (having regard to the dosage amount required).

[0106] Another such formulation is:

Formulation 2

[0107]

Formula	Supplier	(LOT)	Amount	Percent
Methoxypolyethylene Glycol 350	Sigma	34F-0266	300 g.	20
Benzyl Alcohol	BDH	23797	15 g.	1
Diclofenac Sodium	Prosintex	9123012	45 g.	3
Sodium Hyaluronate (MW 679,000)	Skymart	HG 1004	37.5 g.	2.5

(continued)

Formula	Supplier	(LOT)	Amount	Percent
Sterile Water balance	Baxter	AW45R6	1200 ml.	

Procedure

[0108]

- set up stirring apparatus using a 3 litre stainless steel beaker
- add water, Methoxypolyethylene Glycol 350, and Benzyl Alcohol and stir for 20 minutes to mix
- add Diclofenac Sodium and stir for 30 minutes to dissolve
- add Hyaluronate Sodium slowly and stir initially at a high speed, but avoid splashing
- after addition, stir at a slower speed for 90 minutes; the slower speed reduces the formation of air bubbles
- the result is a clear, transparent, viscous gel which is put into a container. Once again instructions are given for administration and if applicable measuring devices (to provide a premeasured dosage amount) accompany the container.

[0109] Still other formulations are:

Formulation 3

[0110]

3% Diclofenac in 2.5% HA Gel				
Formula	Supplier	LOT	Amount	Percent
Sterile Water	Baxter	AW45K6	1200 ml	-
Methoxypolyethylene Glycol 350	Sigma	34F-0266	300G (273 ml)	20%
Benzyl Alcohol	BDH	23797	15G (14 ml)	1%
Diclofenac Sodium	Prosintex	9123012	45 g	3%
Sodium Hyaluronate MW 679,000	Skymart	HG 1004	37.5 g	2.5%

Procedure

[0111]

- Set up stirring apparatus using a 2 liter stainless steel beaker,
- Add water, Methoxypolyethylene Glycol 350, and Benzyl Alcohol and stir for 20 minutes to mix,
- Add Diclofenoc Sodium and stir for 30 minutes to disolve,
- Add Hyalaronate Sodium slowly and stir initially at a high speed, but avoid splashing,
- After addition, stir at a slower speed for 90 minutes,the slower speed reduces the formation of air bubbles,
- The result is a clear transparent, viscous gel which is poured into jars and tubes. Once again instructions accompany the container and where applicable appropriate devices for providing a premeasured amount of the composition accompany the container.

Formulation 4

[0112]

5% IBUPROFEN IN 3.0% HA GEL, 50 ml JAR				
Formula	Supplier	LOT	Amount	Percent
Sterile Water	Baxter	AW45R6	196 ml	--
Meglumine	Falk	15684	11 g	5.5%
Ibuprofen	BDH	19/241	10 g	5%

(continued)

5% IBUPROFEN IN 3.0% HA GEL, 50 ml JAR				
Formula	Supplier	LOT	Amount	Percent
Benzy Alcohol	BDH	23797	2 g	1%
Glycerin	BDH	2579	2 g	1%
Hyaluronate Sodium Mol Wt 661,600	Skymart	HG 1003	6 g	3%

PROCEDURE

[0113]

- Set up stirring apparatus using a 300 ml stainless steel beaker,
- Add Sterile Water and Meglumine, and stir for 10 minutes,
- Add Ibuprofen and stir for 15 minutes,
- Add Benzyl Alcohol, followed by Glycerin and stir for 15 minutes,
- Finally, add Hyaluronate Sodium slowly and stir initially at a high torque to mix, but avoid splashing,
- As the gel thickens, stir at a slow speed for 90 minutes.

Formulation 5

[0114]

2% PIROXICAM IN 2.5% HA GEL				
Formula	Supplier	LOT	Amount	Percent
Sterile Water	Baxter	AW45R6	200 ml	--
Meglumine	Falk	15684	8 g	4%
Piroxicam	AMSA	1-010	4 g	2%
Hyaluronate Sodium MW 661,600	Skymart	HG 1003	5 g	2.5%

PROCEDURE

[0115]

- Set up stirring apparatus using a 300 ml stainless steel beaker,
- Add 200 ml of sterile water.
- Add 8 grams of Meglumine and dissolve.
- Very slowly add 4 grams of Piroxicam and stir for 20 minutes,
- Slowly add 5 grams of Hyaluronate Sodium and stir at high speed,
- Stir for 90 minutes at a slower speed

COMMENTS

[0116]

- A clear yellowish transparent gel

Formulation 6

[0117]

5% IBUPROFEN CREAM, 50 ml JAR				
OILY PHASE				
Formula	Supplier	LOT	Amount	Percent
Liquid wax DICDD	Brooks	L-1424	450 g	15%
Brookswax D	Brooks	P-490	480 g	16%
Glycerin	BDH	109109/2578	150 g (119 ml)	5%
AQUEOUS PHASE				
Sterile Water	Baxter	AW45F1	1950 ml	--
Meglumine	Falk	15684	150 g	5%
Ibuprofen MW 200,00	BKH	19/241	150 g	5%
Sodium Hyaluronate	Skymart	001	45 g	1.5%
Preservative Suttocide	A Sutton	SH-107	9 g	0.3%

PROCEDURE

[0118]

A - Add all the ingredients of the oily phase A into a 4 liter stainless steel beaker, melt at 55°c, finally heat to 75% when Aqueous Phase B is ready
B - Into a 3 liter stainless steel beaker, add 1950 ml water, set up, the stirring apparatus, add the Meglumine, stir to dissolve for 10 minutes.

- Slowly add Ibuprofen, stir to dissolve for 20 minutes,
- Very slowly add Sodium Hyaluronate and stir for one hour to dissolve all the Sodium Hyaluronate,
- Finally, heat to 75°C, with stirring for a total time of 30 minutes.

POUR B INTO A, both at a temperature of 75°C, slowly

[0119]

- Remove the heat source and stir with a strong vortex for one hour,
- When the temperature has cooled down to 45°C add preservative Suttocide A,
- Continue stirring at a slower speed until the temperature is 35°C,
- At 35°C remove the propeller, pour into 50 ml jars.

Formulation 7

[0120]

1% DICLOFENAC IN 3% HA Gel, 50 ml jar				
Quantity 3000ml				
Formula	Supplier	LOT	Amount	Percent
Sterile Water	Baxter	AW45R6	2796ml	-%
Glycerin	BDH	2579	50g(71ml)	3%
Benzyl Alcohol	BDH	23797	45g(43ml)	1.5%
Liquid wax DICDD	Brooks	191-175	90 g	3%
Diclofenac Sodium	Prosintex	9113003	30 g	1%
Hyaluronate Sodium MW 679,000	Skymout	HG 1004	90 g	3%

PROCEDURE

[0121]

- Set up stirring apparatus using a 4 liter stainless steel beaker.
- Add water, Glycerin, Benzyl Alcohol and Liquid wax DICDD and stir to mix thoroughly for 10 minutes
- Add Diclofenac Sodium and stir for 30 minutes to dissolve.
- Slowly add Hyaluronate Sodium, stirring at a high torque initially during addition.
- After addition stir at a slower speed for 90 minutes.
- A white opaque viscous gel is formed.

Formulation 8

[0122]

1% DICLOFENAC IN 3.0% HA Gel, 50 ml tube				
Quantity 1500 ml				
Formula	Supplier	LOT	Amount	Percent
Sterile Water	Baxter	AW45F1	1397 ml	-%
Glycerin	Life	1043	45g(36 ml)	3%
Benzyl Alcohol	Caledon	02517	22.5g(22ml)	1.5%
Liquid wax DICDD	Brooks	191-175	45 g	3%
Diclofenac Sodium	Prosintex	9113003	15 g	1%
Sodium Hyaluronate Mol. Wt. 661,600	Skymart	HG 1003	45 g	3%

PROCEDURE

[0123]

- Set up stirring apparatus using a 3 liter stainless steel beaker.
- Add water, Glycerin, Benzyl Alcohol and Liquiwax DICDD, stir to mix for 10 minutes.
- Add Diclofenac Sodium and stir for 30 minutes to dissolve.
- Add Sodium Hyaluronate and stir for 90 minutes.

Formulation 9

[0124]

HYANALGESE CREAM (L)				
50 ml tube Quantity 3000 ml				
FORMULA				
A. Oily Phase	SUPPLIER	LOT	AMOUNT	PERCENT
Liquid Wax DICDD	Brooks/Amisol		450g	15.0%
Brookswax D	Brooks/Amisol		480g	16.0%
Glycerine	Amisol		150g	5.0%
B. Aqueous Phase				
Sterile Water	Baxter	AW4YA8	1950ml	-%
Meglumine	Falk		150g	5.0%
Sodium Hyaluronate MW 207,000	Skymart	PO1	45g	1.5%
Ibuprofen	BDH		150g	5.0%

(continued)

HYANALGESE CREAM (L)				
50 ml tube Quantity 3000 ml				
B. Aqueous Phase				
Suttocide A	Sutton		9.0g	0.3%

PROCEDURE

[0125]

A. - Add all the ingredients of the oily phase into a 4 liter stainless steel beaker, melt at 55°C, finally heat to 75°C when aqueous phase is ready (at 75°C) to pour in.
B. - Into another 4 liter stainless steel beaker, add 1950 ml water.

- Set up the stirring apparatus and add the Meglumine
- Stir to dissolve with high torque, then slowly add Ibuprofen
- When the Ibuprofen is dissolved, slowly add Sodium Hyaluronate
- Stir cold for one hour to dissolve all the ingredients
- Finally heat to 75°C and stir thoroughly throughout a 30 minute period

MIX B INTO A

[0126]

- Slowly pour B into A (both at 75°C) with stirring
- Immediately remove the hot plate (heat) and stir
- Stir with a strong vortex for one hour
- When the temperature is 45°C, add the preservative Suttocide A
- Stir for about an hour to cool to 35°C
- At 35°C remove the propeller and pour into 50 ml tubes
- Pour 50 grams of the cream into each tube

1% BANAMINE IN 2.5% HA GEL				
(L) XPB 041	Quantity 3000 ml			
FORMULA				
	SUPPLIER	LOT	AMOUNT	PERCENT
Sterile Water	Boxter	AW4SA2	2400 m	1--%
Sodium Hyaluronite MW 661,600	Skymart	HE1003	75g	2.5%
*Banamine, 100 ml vial	Scheing	O CNXB13	300 ml	1%
Banamine, 100 ml vial	Scheing	O CNXB12	300 ml	1%
			3000 ml	
(50 mg/ml) 600 = 30,000mg = 30 grams Flunixin in 600 ml				

*Banamine contains Flunixin Meglumine (50 mg Flunixin per ml) or 83 mg Flunixin Meglumine

PROCEDURE

[0127]

- Set up stirring apparatus using a 4 liter stainless steel beaker

- Add water, stir with a strong vortex, then add sodium Hyoluronate slowly
- Then immediately add the Banamine, stir the mixture for 4 hours.

[0128] One form of hyaluronic acid and/or salts thereof (for example sodium salt) and homologues, analogues, derivatives, complexes, esters, fragments, and sub-units of hyaluronic acid, preferably hyaluronic acid and salts and thereof, suitable for use with Applicant's invention is a fraction supplied by Hyal Pharmaceuticals Limited. One such fraction is a 15 ml vial of Sodium hyaluronate 20mg/ml (300mg/vial - Lot 2F3). The sodium hyaluronate fraction is a 2% solution with a mean average molecular weight of about 225,000. The fraction also contains water q.s. which is triple distilled and sterile in accordance with the U.S.P. for injection formulations. The vials of hyaluronic acid and/or salts thereof may be carried in a Type 1 borosilicate glass vial closed by a butyl stopper which does not react with the contents of the vial.

[0129] The fraction of hyaluronic acid and/or salts thereof (for example sodium salt) and homologues, analogues, derivatives, complexes. esters, fragments, and sub-units of hyaluronic acid, preferably hyaluronic acid and salts thereof, may comprise hyaluronic acid and/or salts thereof having the following characteristics:

a purified, substantially pyrogen-free fraction of hyaluronic acid obtained from a natural source having at least one characteristic selected from the group (and preferably all characteristics) consisting of the following:

i) a molecular weight within the range of 150,000-225,000;
ii) less than about 1.25% sulphated mucopolysaccharides on a total weight basis:
iii) less than about 0.6% protein on a total weight basis;
iv) less than about 150 ppm iron on a total weight basis;
v) less than about 15 ppm lead on a total weight basis:
vi) less than 0.0025% glucosamine;
vii) less than 0.025% glucuronic acid;
viii) less than 0.025% N-acetylglucosamine;
ix) less than 0.0025% amino acids;
x) a UV extinction coefficient at 257 nm of less than about 0.275;
xi) a UV extinction coefficient at 280 nm of less than about 0.25; and
xii) a pH within the range of 7.3-7.9. Preferably, the hyaluronic acid is mixed with water and the fraction of hyaluronic acid has a mean average molecular weight within the range of 150,000-225,000. More preferably, the fraction of hyaluronic acid comprises at least one characteristic selected from the group (and preferably all characteristics) consisting of the following characteristics:

i) less than about 1% sulphated mucopolysaccharides on a total weight basis;
ii) less than about 0.4% protein on a total weight basis,
iii) less than about 100 ppm iron on a total weight basis;
iv) less than about 10 ppm lead on a total weight basis;
v) less than 0.00166% glucosamine;
vi) less than 0.0166% glucuronic acid;
vii) less than 0.0166% N-acetylglucosamine;
viii) less than 0.00166% amino acids:
x) a. UV extinction coefficient at 257 nm of less than about 0.23;
xi) a UV extinction coefficient at 280 nm of less than 0.19, and
xii) a pH within the range of 7.5-7.7

[0130] Applicants also propose to use sodium hyaluronate produced and supplied by LifeCore™ Biomedical, Inc., having the following specifications:

Characteristics	Specification
Appearance	White to cream colored particles
Odor	No perceptible odor
Viscosity Average Molecular Weight	< 750,000 Daltons
UV/Vis Scan, 190-820nm	Matches reference scan
OD, 260nm	< 0.25 OD units

(continued)

Characteristics					Specification			
Hyaluronidase Sensitivity					Positive response			
IR Scan					Matches reference			
pH, 10mg/g solution					6.2 - 7.8			
Water					8% maximum			
Protein					< 0.3 mcg/mg NaHy			
Acetate					< 10.0 mcg/mg NaHy			
Heavy Metals, maximum ppm								
As	Cd	Cr	Co	Cu	Fe	Pb	Hg	Ni
2.0	5.0	5.0	10.0	10.0	25.0	10.0	10.0	5.0
Microbial Bioburden					None observed			
Endotoxin					< 0.07EU/mg NaHy			
Biological Safety Testing					Passes Rabbit Ocular Toxicity Test			

[0131] Another form of sodium hyaluronate is sold under the name Hyaluronan HA-M5070 by Skymart Enterprises, Inc. having the following specifications:

Specifications' Test	
Results	
Lot No.	HG1004
pH	6.12
Condroitin Sulfate	not detected
Protein	0.05%
Heavy Metals	Not more than 20 ppm
Arsenic	Not more than 2 ppm
Loss on Drying	2.07%
Residue on Ignition	16.69%
Intrinsic Viscosity	12.75 dl/s (XW: 679,000)
Nitrogen	3.14%
Assay	104.1%
Microbiological Counts	80/g
E. coli	Negative
Mold and Yeast	Not more than 50/g

[0132] Other forms of hyaluronic acid and/or its salts, and homologues. derivatives. complexes, esters, fragments and sub units of hyaluronic acid may be chosen from other suppliers. for example those described in prior art documents provided the form of hyaluronic acid chosen is suitable for transport of the medicine.

[0133] The following references teach hyaluronic acid, sources thereof, and processes for the manufacture and recovery thereof which may be suitable.

[0134] United States Patent 4,141,973 teaches hyaluronic acid fractions (including sodium salts) having:

"(a) an average molecular weight greater than about 750,000, preferably greater than about 1,200,000 - that is, a limiting viscosity number greater than about 1400 cm^3/g , and preferably greater than about 2000 cm^3/g.;
(b) a protein content of less than 0.5% by weight;
(c) ultraviolet light absorbance of a 1% solution of sodium hyaluronate of less than 3.0 at 257 nanometers wavelength and less than 2.0 at 280 nanometers wavelength;

(d) a kinematic viscosity of a 1% solution of sodium hyaluronate in physiological buffer greater than about 1000 centistokes, preferably greater than 10,000 centistokes;
(e) a molar optical rotation of a 0.1 - 0.2% sodium hyaluronate solution in physiological buffer of less than -11 X 10^2 degree - cm^2/mole (of disaccharide) measured at 220 nanometers;
(f) no significant cellular infiltration of the vitreous and anterior chamber, no flare in the aqueous humour, no haze or flare in the vitreous, and no pathological changes to the cornea, lens, iris, retina, and choroid of the owl monkey eye when one milliliter of a 1% solution of sodium hyaluronate dissolved in physiological buffer is implanted in the vitreous replacing approximately one-half the existing liquid vitreous, said HUA being
(g) sterile and pyrogen free and
(h) non-antigenic."

[0135] Canadian Letters Patent 1,205,031 (which refers to United States Patent 4,141,973 as prior art) refers to hyaluronic acid fractions having average molecular weights of from 50,000 to 100,000; 250,000 to 350,000; and 500,000 to 730,000 and discusses processes of their manufacture.

[0136] In order to determine the blood levels in patients using formulations made according to embodiments of the invention, a study of the pharmacokinetic profiles of two topical diclofenac formulations after repeat dosing were undertaken.

[0137] One such product was the product Voltarol Emulgel marketed in the United Kingdom by Geigy. The other was a Diclofenac preparation in Hyaluronic Acid.

[0138] This was an open, repeat dose, crossover comparison using a randomized balanced block in six healthy volunteers.

[0139] The study consisted of administration with one, two week period in between periods, each period lasting fourteen days. The test articles applied were for the first six days of each period and the seventh day was study day during which the final application is made and blood samples taken.

[0140] The approximate duration of the study including pre and post study screening was six weeks.

Doses

[0141] Diclofenac (3.0%) with Hyaluronic Acid (2.5%)
Dose: Approximately 2 g, three times daily
Route: Topical

[0142] (W1)Voltarol Emulgel, Diclofenac diethylammonium salt 1.16g aqueous gel (Geigy)
Dose: Approximately 2 g, three times daily
Route: Topical (W1)

ADMINISTRATION: to suitable patients

[0143] Subjects applied one of the designated test articles topically to the calves and massaged into the skin, in a dose of approximately 2 g per application three times a day for six consecutive days. The size of a 2g dose was prepared by comparison with a silicone example given to each subject.

[0144] On the seventh day, the cream was applied once, in the same manner as before, under the supervision of the staff of the Clinical Investigation Unit.

[0145] After a washout period of one week the procedure was repeated with the alternate test article.

[0146] The following were the results of the tests:
(H = hyaluronic acid formulation)
(V = Voltarol Emulgel)

PERIOD 1												
All concentrations ng ml $^{-1}$												
SUBJECT				TIME POINT (hours)								
	0	0.25	0.5	1	2	3	4	5	6	8	10	12
H-1	10.3	7.1	6.4	ND	ND	5.4	6.5	5.1	ND	ND	ND	ND
H-2	ND	5.1	ND	5.1	ND	ND	ND	ND	ND	5.1	ND	ND
ND	ND	ND	5.5	5.2	ND	ND	ND	ND	ND	ND	ND	V-3

(continued)

PERIOD 1													
SUBJECT	TIME POINT (hours)												
	0	0.25	0.5	1	2	3	4	5	6	8	10	12	
ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	H-4	
ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	V-5	
ND	ND	ND	ND	ND	ND	ND	8.4	ND	ND	ND	ND	V-6	
ND = NONE DETECTED (>5.0 ng ml^{-1})													

PERIOD II												
All concentrations ng ml -1												
SUBJECT	TIME POINT (hours)											
	0	0.25	0.5	1	2	3	4	5	6	8	10	12
V-1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
V-2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
H-3	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
V-4	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
H-5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
H-6	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
ND = NONE DETECTED (>5.0 ng ml^{-1})												

[0147] Other tests were undertaken to determine blood levels comparing Proflex (a formulation containing Ibuprofen) and the following formulation containing hyaluronic acid and Ibuprofen

HYANALGESE CREAM (L) X PB 022 - 50 ml tube				
	Quantity 3000 ml			
FORMULA				
A. Oily Phase	SUPPLIER	LOT	AMOUNT	PERCENT
Liquid Wax DICDD	Brooks/Amisol		450g	15.0%
Brookswax D	Brooks/Amisol		480g	16.0%
Glycerine	Amisol		150g	5.0%
B. Aqueous Phase				
Sterile Water	Baxter	AW4YA8	1950ml	-%
Meglumine	Falk		150g	5.0%
Sodium Hyaluronate MW 207,000	Skymart	PO1	45g	1.5%
Ibuprofen	BDH		150g	5.0%
Suttocide A	Sutton		9.0g	0.3%

[0148] The following were the results

(A) PROFLEX													
SUBJECT Number				Time after administration (Hours)									
PD	0	0.25	0.5	1	2	3	4	5	6	8	10	12	
1	NO	0.41	0.37	0.37	0.32	0.30	0.27	0.27	0.24	0.37	0.31	0.31	0.16
2	ND	0.12	0.12	0.08	0.11	0.12	0.12	0.07	0.08	0.09	0.08	ND	0.06

(continued)

(A) PROFLEX													
SUBJECT Number				Time after administration (Hours)									
PD	0	0.25	0.5	1	2	3	4	5	6	8	10	12	
3	DD	0.09	0.08	0.07	ND	ND	ND	ND	ND	ND	ND	ND	ND
4	ND	0.12	0.14	0.16	0.11	0.11	0.25	0.24	0.17	0.13	0.16	0.11	0.13
5	ND	0.14	0.19	0.19	0.15	0.16	0.16	0.14	0.12	0.11	0.13	0.10	0.07
6	ND	0.11	0.09	0.09	0.06	0.07	0.05	0.05	0.05	ND	ND	ND	ND
Mean	0.00	0.17	0.17	0.16	0.13	0.13	0.14	0.13	0.11	0.12	0.11	0.09	0.07
S.D.	0.00	0.12	0.10	0.11	0.10	0.10	0.10	0.10	0.08	0.13	0.11	0.12	0.06

(B) HYALURONIC ACID AND IBUPROFEN													
SUBJECT Number				Time after administration (Hours)									
	PD	0	0.25	0.5	1	2	3	4	5	6	8	10	12
1	ND	0.11	0.11	0.12	0.08	0.08	0.09	0 11	0.12	0.08	0.11	0.16	0.14
2	ND	0.22	0.21	0.26	0.17	0.24	0.24	0.25	0.23	0.19	0.19	0.20	0.14
3	ND	0.17	0.10	0.12	0.09	0.08	0.07	0.06	ND	0.06	0.26	0.09	0.05
4	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
5	ND	0.17	0.16	0.16	0.12	0.09	0.10	0.11	0.10	0.09	0.10	0.07	ND
6	ND	0.07	0 07	0.09	ND	ND	ND	ND	ND	ND	ND	ND	ND
Mean	0.00	0.12	0.11	0.13	0.08	0.08	0.08	0.09	0.08	0.07	0.11	0.09	0.06
S.D.	0.00	0.08	0.07	0.08	0.06	0.08	0.08	0.09	0.09	0.07	0.10	0.08	0.07
ND None detected <0.05 μg/ml													

[0149] The above clearly indicates that the blood levels are much less using hyaluronic acid to administer the NSAID.

PRELIMINARY REPORT

[0150] A trial was conducted using a gel composition (Number 109) comprising 3% Diclofenac in 2.5% Hylauronic Acid as previously described and a composition containing Diclofenac sodium salt 3% but not including any form of hyaluronic acid. (Number 112) The trial was conducted with 60 patients who were randomly assigned to test preparations number 109 or 112. The trial has not been completed as yet but so far 31 patients have finished the protocol. Patients were diagnosed:

4 Rheumatoid arthritis of the knee
8 Myofascial trigger points in the M.trapezius area
12 Periarthropathies of knee without effusion
7 Periarthropathies with effusion in the knee joint

[0151] The 31 patients were aged 22-75 years (27 females, 4 males). All patients were hospitalized. Patients entering the trial were thoroughly examined and type of extraarticular or articular rheumatism assessed.

[0152] On day 1 baseline pain was assessed on the 10 cm visual analogue scale (VAS) and pain measurement of the quantititative pain sensitivity using a pressure tolerance meter (PTM) were performed. Then test gel - approximately 2.g - was massaged on to the skin of maximum pain. Gels were applied 3 times daily.

[0153] 0.5, 1, 1.5, and 2 hours after morning application measurements of pain sensitivity were carried out and values recorded.

[0154] This procedure was countinued on day 2, 3 and 4; measurements (VAS and PTM) of pain severity were done on day 1, 2 and 4.

[0155] Prior of the beginning of the study and at the end on day 4, physician's global assessment, assessment of swelling, tenderness and limitation of movement were recorded.

[0156] As the study is ongoing statistical evaluation is not yet available. For further details see Table 1.

TABLE 1

	Composition	Composition
Reaction	109, n = 16	112, n - 15
Good Alleviation of pain	13	8
Moderate Alleviation of pain	2	2
No Alleviation of pain	1	5

[0157] From the data recorded we have concluded that the patients to whom composition 109 was administered did better in terms of earlier and longer lasting analgesic effect (up to 4 hours) than the 112 composition especially in patients with myofascial trigger points and with periarthropathies of the knee joints without effusions. Neither composition 109 nor composition 112 treated patients showed any effect on swelling if any swelling exist at all. Systemic side effects have not been observed; one patient to whom composition 112 was administered showed reddening of the skin on the site of application.

[0158] Any intake of system NSAIDS,corticosteroids and other analgesics was not allowed one week before and during the trial.

EXAMPLES

[0159] The following examples are offered to illustrate uses of Applicants' invention.

Example 1

[0160] A male patient had a number of lesions (basal cell carcinoma), including one on his forehead which was a combination of major "horny epithelium" and some degree of ulceration. After continuous treatment with Formulation 1 (several times per day for several weeks of dosage amounts squeezed from tubes as ribbons of composition), the lesions showed epithelialization, no hemorrhagic areas, and no initiated areas (as they were in the past without our treatment). The "horny epithelium" and ulceration of the forehead lesion were also gone. The patient had a complete successful response with the formulation. All basal cell carcinoma lesions had been resolved and disappeared. There has been no recurrence.

Example 2

[0161] 60 year old male tennis player had sore elbow and basal cell carcinoma on forearm proximate sore elbow. Patient tried Formulation 1 to abate pain in tennis elbow. (Dr. Falk was not treating this patient for anything at the time, did not know of the basal cell proximate the elbow and merely offered the formulation for pain relief of the elbow instucting the patient to squeeze a ribbon of the composition and apply and rub into the sore elbow). However, the formulation "spilled" over onto the Patient's basal cell carcinoma. Patient was planning to have basal cell carcinoma removed surgically by another doctor, but when the patient returned to see the doctor, the basal cell carcinoma was disappearing (because of spill-over of Formulation 1). Dr. Falk was then advised and treatment was now undertaken by Dr. Falk with direct application of Formulation 1 to the lesion 3 times a day for two additional weeks. After two weeks, the basal cell carcinoma disappeared. There has been no recurrence.

Example 3

[0162] Male, mid to late 40's had severe basal cell carcinoma on left temple. Doctors recommended its removal by surgery. However, the surgery would have been risky because of the lesion's proximity to facial nerves.

[0163] Patient saw Dr. Falk who gave him Formulation 2 to be applied in dosage amounts 3 times daily.

[0164] After 14 days, 75% of the lesion was gone. Surgery was postponed and the treatment was continued. Application of dosage amounts of Formulation 2 was continued for an additional two weeks. At the end of the 2- week period, the lesion was completely resolved and disappeared without any surgery being required. There has been no recurrence.

Example 4

[0165] Male, early 40's, had recurrent actinic keratoses lesion on his right temple. Early attempts at removal by third

parties involved the application of liquid nitrogen (twice) without final resolution. The lesion kept recurring. The patient was sent to Dr. Falk who treated the lesion with Formulation 1 with applications of dosage amounts 3 times daily for 7 days. After 7 days, the lesion was completely resolved with no subsequent recurrence.

Example 5

[0166] A male patient suffering from kyphosis suffered from constant back pain. Taking analgesics orally and rubbing back preparations onto his back did little to alleviate the back pain. When NSAIDs in hyaluronic acid (sodium hyaluronate) were applied directly to the back, the back pain eased and disappeared.

[0167] With indomethacin (dissolved in N-methyl glucamine) and naproxen both dissolved in hyaluronic acid, the patient experienced some side effects. However, with Toradol™ (the [+/-] form tromethamine salt of ketorolac - a prostaglandin biosynthesis inhibitor and analgesic and anti-inflammatory, the back pain eased and disappeared for some time and there were no side effects. The compositions were applied generously onto the sites of back pain.

Example 6

[0168] A male patient with basal cell carcinoma was first treated by an oncologist who attempted to surgically excise the lesion (without success) and then irradiated the lesion again without success. The patient then attended before Dr. Falk who applied Applicant's formulation (diclofenac with sodium hyaluronate and excipients). Application was made three times daily for about a month and the lesion disappeared. Some excoriation anterior and slightly superior developed over the last two weeks but was cleared by the application of hyaluronic acid by itself.

[0169] This resolution clearly indicates that even with prior applications of unsuccessful therapies (surgery and irradiation), Applicant's formulations can be used successfully.

Example 7

[0170] In another patient, a drug (methotrexate) was carried in hyaluronic acid and applied topically to a patient with psoriasis. The formulation was absorbed and the psoriasis cleared.

Example 8

[0171] A patient with dermal (skin) metastases in a fibratic scar form and metastatic cancer in the form of musculoskeletal involvement in her thorax.

[0172] On topical application of our formulation comprising diclofenac (Voltaren) in hyaluronic acid (sodium hyaluronate), her pain decreased dramatically and her skin and boney involvements steadily improved.

TOPICAL DICLOFENAC ACID 3% IN HYALURONIC ACID GEL (2.5%) BASE

[0173] A practitioner reviewed the effectiveness of topical Diclofenac Acid 3% in hyaluronic acid gel (2.5%) base in acute traumatic injuries of no longer than 3 days duration. The cases were all in the spectrum of ages between 18 and 65. Normal exclusion criteria were followed regarding exclusion of pregnancy, aspirin or N.S.A.I.D., allergies or active peptic ulceration.

[0174] As an overall, the following impressions were gained from 30 cases :

1. The topical H.D.(composition comprising sodium hyaluronate and diclofenac) had an obvious analgesic action with onset occurring rapidly within one hour; this is a phenomenon not obviously seen with other non-steroidals that we have used.
2. There was a very definite patient acceptance of the gel as a form of treatment, being logical, easy to apply, without local or systemic side effects, rapid absorption with no staining of clothing.
3. The anti-inflammatory action was equivalent on a "guestimate" based on experience of similar injuries to oral N.S.A.I.D.s, without the threat or risk of side effects.

[0175] In summary, compared with other topical N.S.A.I.D.s the analgesic effect is distinct, the anti-inflammatory is equal to oral N.S.A.I.D.s and the patients' acceptance is far superior to any other diclofenac or piroxicam topical that the practitioner evaluated.

[0176] Following the practitioner's basic preamble regarding the parallelism of topical N.S.A.I.D.s and topical steroids, the practitioner has used the former in contact dermatitis, insect bites and U.V. erothema, all with very positive effects, again pointing direction to trials of a double blind nature in these fields.

CHRONIC CONDITIONS - EVALUATIONS					
2.5% HYALURONIC ACID WITH 3% DICLOFENIC ACID (HD)					
Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
LA (M)	11.04.56		Hyper-aesthesia	Severe discomfort following extensive surgery to dorsal spine with insertion of rods in 1989. Even contact with clothes produced significant discomfort. Initially treated with EMLA with only transient anaesthetic results, however even after 3 days treatment with Hyal diclofenac acid noticed marked decrease in supersensitivity which has continued for at least 4 weeks while still using gel.	P Example of peripheral action on supersensitization of nerve ending queried.
KB (F)	08.06.58		Chronic chondromalacia perhaps dating back to 1976.	Treated right knee which was worse initially and was amazed at the response, then started to treat left knee that was not so painful, again with positive response. Here we have a built-in control.	P
DB (F)			Chronic neurogenic pain in ankle with associated dysaesthesia.	Initially felt some improvement which was not continued although initially quite positive - query placebo reaction.	N

(continued)

CHRONIC CONDITIONS - EVALUATIONS					
2.5% HYALURONIC ACID WITH 3% DICLOFENIC ACID (HD)					
Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
DC (F)	07.11.51		Chronic back pain - query due to facet syndrome or trigger points, really diagnosis uncertain.		N

CHRONIC CONDITIONS - EVALUATIONS					
HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)					
Patients Initials (M) or (F)	Date Of Birth	File No	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
∝	18.01.25		Chronic cap-sulitis right hip right knee	Definite effect over knee where application to target distance short. No obvious effect over hip.	P
AG (F)	07.11.58		Myositis in rhomboids muscles following motor vehicle accident	Initially given placebo in error, only marginal or minimal effect, if any. Found active to be effecttive while being used, did not cure condition which needed trigger point therapy.	P
CH (F)	22.08.61		Chronic relapsing tendonitis right elbow	No significant effect, nor has aggressive therapy since including injection with cortisone and numerous opinions.	N

(continued)

CHRONIC CONDITIONS - EVALUATIONS					
HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)					
Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
SH (F)	16.07.55		Tendonitis and myositis	Control of tendonitis while using preparation. Is now back at work.	P
DM (M)	17.06.47		Neuronitis	This patient has a very unusual pain in his left groin following nerve injury, with the use of preparation noticed decrease in pain sensation while on medication. Hyperaesthesia altered although pain (which may be phantom) still present.	U
PJ	15.06.45		Capsulitis of right wrist	Symptoms improved 50% while using Hyal diclofenac acid, however, on discontinuation pain reappeared. Exact etiology uncertain.	U

CHRONIC CONDITIONS - EVALUATIONS					
HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)					
Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
DJ (F)			Dorsal myositis	Control while using gel equal and with less side effects than tiger balm. Controlled symptoms while using medication. Exact diagnosis as to cause of myositis uncertain.	P
DK (F)	27.08.38		Severe capsulitis left shoulder	This patient has had capsulitis left shoulder for many years and treated with only transient relief with cortisone injections. poor relief with topical piroxicam. Was started on topical diclofenac acid and noticed relief of pain in 20 minutes continuing for 4 - 6 hours. See letter March 11/92. At present is using H. D. regularly. has found it to be useful in other areas of chronic pain. Is President North American Chronic Pain Association. has good insight into medication and placebos etc. Has two D.C.S. implants.	P Extremely rewarding case

CHRONIC CONDITIONS - EVALUATIONS					
HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)					
Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
JL (M)	10.12.45		Chronic myositis secondary to query facet syndrome	Pain has failed to respond to many aggressive treatments.	N
RMC(F)	13.06.57		Neuronitis following facet rhizotomy with resulting pain in her back	It is a difficult case with considerable overlay, she obtained some relief with H.D., would estimate 30-40% Interestingly hyper-anaesthesia was decreased.	U
RM (F)	20.08.52		Chronic capsulitis	Using H.D. significant improvement in pain while used, on stopping treatment recurrence of pain, needed intra-articular cortisone.	P
GM (F)			Sub-acute tendonitis right ankle	Rapid resolution of pain within one day and positive return of function.	P
PM (F)	20.09.46		Acute on chronic osteo-arthritis of first metatarsal phalyngeal joints	Rapid analgesic response with rapid settlement.	P
DN (F)	10.03.44		Chronic fasciaitis of feet	Excellent response to application of H. D. with occlusion. Had failed to respond to oral N. S.A.I.D.s and physiotherapy. Query positive result due to short application target distance in a vascular tissue.	P

CHRONIC CONDITIONS - EVALUATIONS					
HYALURONIC ACID WITH 3% DICLOFENIC ACID (HD)					
Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
BP (F)	04.03.20		Severe chronic arthritis of the knee. Unable to take oral N.S.A.I.D.s	Initially one knee treated with such good results that both knees treated, see letter. Not only did pain decrease but marked swelling around knees. Significant relief of pain and increase in movement as a result of this and perhaps reduction of swelling. Intrestingly has severe superficial varicose veins, developed thrombophlebitis around right knee and the area treated by chance showed far less redness and tenderness than the thrombophlebitis below this area.	P Side effects-non/ Incidental resolution of area of thrombophlebitis below area of treatment
SP (M)	06.11.48		Idiopathic diffuse capsulitis of hands	Has had similar episodes with poor response to many treatments including N. S.A.I.D.s per os	U
WS	04.06.45		Chronic neuronitis due to injury to lateral cutaneous nerve of thigh	Has been exposed to numberous treatments including tow attempts of surgery without effect. There is decrease in hyperaesthesia but no change in pain.	U
MS (F)	04.06.28		Chronic capsulitis	Failed to respond to number of treatments, good background resolution of pain, however, still had acute pain with certain movements.	P

CHRONIC CONDITIONS - EVALUATIONS					
HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)					
Patients Initials (M) or (F)	Date Of Birth	File No	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
IS (F)	15.01.48		Chronic capsulitis	Had failed to respond to numerous treatments including oral and topical N.S.A.I.D.s Using H.D there was equivalent control of pain as with other therapies which lasted while medication was used. Referred for surgical opinion.	P
GS (F)	26.03.47		Chronic tendosinovitis tion.	Oral diclofenac acid discontinued due to gastritis and also history of ulceration. Control using H.D equal to or better than oral N.S.A.I.D.s.	P
VK (F)	01.01.39		Chronic tendonitis	Good relief of pain and tenderness while using H.D. however on discontinuation of gel symptoms returned, treated with intramuscular steroids.	P for pain N for resolution
GH (M)	03.11.21		Acute on chronic osteoarthritis left hand	In view of age and general parous medical condition, ideal for topical. Had been previously on topical piroxicam for left shoulder capsulitis.	P Commented on better absorption compared to topical piroxicam

CHRONIC CONDITIONS - EVALUATIONS					
HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)					
Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
JA (M)	06.02.58		Severe post-traumatic and surgical osteoarthritis of left leg with staples. Poor result to oral N.S.A.I.D.s also gastric irritation.	Produced good superficial analgesia especially where staples were irritating subcutaneous tissue, little effect on deeper, severe osteoarthritic pain of knee. This pain was of considerable severity, needing narcotics.	P
IM (M)	30.11.51		Chronic superficial myositis	Severe rhomboid inflammation right side, treated with H.D., very definite improvement in pain and tenderness.	P
TK (F)	23.04.70		Acute on cnronic capsulitis due to sports injury right hand	Excellent rapid analgesic followed by anti-inflammatory response in young women who could not take oral N.S.A.D.s due to past gastritis.	P
AD (F)	03.01.49		Chronic diffuse pain thought to be myositis	Poor response to H.D. After intensive investigation and numerous consultations and treatment, pain still undiagnosed and unresponsive.	N

(continued)

CHRONIC CONDITIONS - EVALUATIONS					
HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)					
Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
NH (F)	25.03.25		Subacute capsulitis right ankle	Excellent response analgesic and anti-inflammatory-wise within a few days. Marked clinical improvement. In view of this patient's parous general medical condition and hypertension, not suitable for oral NSAIDs.	P

CHRONIC CONDITIONS - EVALUATIONS					
HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)					
Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
MD)	18.04.34		Subacute rheumatoid arthritis	Had failed to respond to oral N. S.A.I.D.s, which caused gastritis, tried on topical piroxicam with negative effects. Negative response to H.D.	N
MW (F)	07.05.46		Heberden's nodes. painful, swollen causing difficulty in movement	Very slow positive outcome. initially improvement in pain followed by reduction in swelling. Etiology of this condition is unknown, partly genetic. Would have been interesting to treat alternate digits, plus or minus thermographic confirmation.	P

(continued)

CHRONIC CONDITIONS - EVALUATIONS					
HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)					
Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
LP (F)	20.07.23		Acute on sub-acute osteoarthritis of the hands with Heberden's nodes	Initially treated with Idarac, poor response overall, some improvement in generalised arthritis of hands but none on Heberden's nodes. Pain flared on stopping Idarac due to gastritis. Started on H.D., especially favourable results with subsidence of tenderness of nodes and settling of arthritis. Interestingly enough, no flare up on discontinuation after one month.	P

CHRONIC CONDITIONS - EVALUATIONS

HYALURONIC ACID WITH 3% DICLOFENAC ACID (HD)

Patients Initials (M) or (F)	Date Of Birth	File No.	Diagnosis	Comments on Outcome	Positive (P) Negative (N) Unable to Comment (U)
JG (F)	24.11.50		Post facet rhizotomy hyperaesthesia. with marked pain and hyperaesthesia between scapulae	Had failed to respond to oral N. S.A.I.D.s and E.M. L.A. Application of H.D. improved the surface pain significantly but had no effect on the deeper pain. My impression was that the deeper pain was due to section of the facet nerve and beyond the reach of the topical medication. There is little doubt that the skin sensitivity was decreased.	U
SW (F)	10.09.39		Knee pain due to chondro malacia	Upset in past due to oral N.S.A.I.D.s., also hypertension made one loathe to use this medication with serum levels. Good analgesic and anti-inflammatory action, however on discontinuation pain flared. Seen for arthroscopic surgery with relief of pain.	P (Effective while being used) Condition only cured by surgery

* Two types of pain-response in only one

1. Interestingly in the whole series, there was not one case of local side effects and as expected from past studies, no general or systemic. Since this report was prepared we have had one case of mild folliculitis which responded to discontinuation of treatment, will rechallenge.
2. A number of patients commented that they felt the gel improved the texture and softness of their skin, and commented that it was messy or stained their clothes.
3. In one case of topical thrombophlebitis where the inflamed vein crossed the area of treatment, the vein in the area of treatment improved while that outside at a distance did not. Again, similar to using oral N S.A I.D s. ***.

[0177] Photographs were taken of patients with basal cell carcinoma Figures 1-6 photographs, and of mice with tumors induced in the skin of the hind legs (Figure 7 photographs). The patients were treated by using combinations of NSAIDS, (non-steroidal anti-inflammatory drugs) and hyaluronic acid (including sodium hyaluronate) according to the invention (3% diclofenac in 2.5% sodium hyaluronate gel base). Each of the six sets of Figures made up of pho-

tographs of the different persons should include a legend describing or explaining each picture as follows:

Legend for Figures 1A and 1B should read:	
Patient	W.D., male, 82 years
Diagnosis	Basal cell carcinoma
Treatment	NSAIDS plus HA gel. 3 times per day
Figure 1A	June, 1991
Figure 1B	December, 1991
Legend for Figures 2A and 2B should read:	
Patient	M.F., male. 45 years
Diagnosis	Basal cell carcinoma
Treatment	NSAIDS plus HA gel. 3 times per day
Figure 2A	January, 1992
Figure 2B	April, 1992
Legend for Figures 3A. 3B, 3C and 3D should read:	
Patient	H.A., male, 82 years
Diagnosis	Basal cell carcinoma
Treatment	NSAIDS plus HA gel. 3 times per day
Figure 3A	January 26, 1992
Figure 3B	March 16. 1992
Figure 3C	January 26, 1992
Figure 3D	March 16.1992
Legend for Figures 4A. 4B, 4C and 4D should read:	
Patient	R.F., male, 64 years
Diagnosis	Basal cell carcinoma
Treatment	NSAIDS plus HA gel. 3 times per day
Figure 4A	January 26, 1992
Figure 4B	March 16. 1992
Figure 4C	January 26, 1992
Figure 4D	March 16. 1992
Legend for Figures 5A. 5B, 5C and 5D should react:	
Patient	R.W., male, 86 years
Diagnosis	Basal cell carcinoma
Treatment	NSAIDS plus HA gel. 3 times per day
Figure 5A	January 26, 1992
Figure 5B	March 16. 1992
Figure 5C	January 26, 1992 untreated
Figure 5D	March 16. 1992 untreated
Legend for Figures 6A. 6B and 6C should read:	
Patient	E.D., female, 70 years
Diagnosis	Basal cell carcinoma
Treatment	NSAIDS plus HA gel. 3 times per day
Figure 6A	April 20, 1992
Figure 6B	May 13, 1992
Figure 6C	July 7, 1992
The Legend for Figure 7 (Figures 7A and 7B) relate to:	
Mouse Strain	DBA_2
Tumour	p815

(continued)

Legend for Figures 5A, 5B, 5C and 5D should react:	
The Legend for Figure 7 (Figures 7A and 7B) relate to:	
Figure 7A	control, 19 days
Figure 7B	Novantrone plus HA gel 19 days

[0178] The mice shown in Figures 7A and 7B had tumours induced in the skin of their hind legs and dosage amounts (2ml) of Novatrone (10 mg. per dosage amount) (MITOXANTRONE (t.m.) and 2.5% sodium hyaluronate were applied (rubbed onto) the skin at the site of the-pathology. The tumours reduced in size (See Figure 7B) clearly illustrating the percutaneous delivery of the medicine by the hyaluronic acid. (See Figure 7).

[0179] The following additional comments are made with respect to the patients.

[0180] With respect to R.W. and Figure 5, the reader will note in Figures 5a and 5c the patient suffered from basal cell carcinoma on his back (Figure 5c) and his temple (Figure 5a). Because of the age of the individual (86) the basal cell carcinoma on his back could not be reached by him for application of the medication. Thus the basal cell carcinoma in 5c remained untreated and grew (see Figure 5d). However, the portion indicated in 5a on his temple could be reached and after application of the basal cell carcinoma formulation to the temple and forehead the results are as in 5b; the basal cell carcinoma is disappearing. Thus, the gentlemen's own method of treatment acted as a control.

[0181] With respect to R.F. and Figures 4, two areas of basal cell carcinoma in need of treatment are shown by the arrows in Figures 4a and 4c and the results are shown in Figures 4b and 4d as indicated by the arrows after treatment with Applicant's invention.

[0182] With respect to H.A., male, and Figures 3, Figures 3 indicates two areas of basal cell carcinoma by the arrows, close-ups of which are shown in Figures 3a and 3c. After treatment with the NSAIDS and HA gel three times a day for the period between January 26, 1992 and March 16, 1992 the basal cell carcinoma is clearing as per Figures 3b and 3d.

[0183] The same is true with respect to male M.F. and Figures 2 which appears clear in the photographs (see Figure 2a and the response shown in Figure 2b).

[0184] With respect to male, W.D. and Figures 1, the upper lesion in Figure 1a (indicated by the upper arrow) is gone after treatment with Applicant's invention (See Figure 1b) and the two lower lesions in Figure Ia are well on their way to disappearing (See Figure 1b).

[0185] With respect to female D and Figure 6, the lesion was left untreated for a long period and gradually encompassed her eye. Surgery could not be undertaken without jeopardizing the eye. By applying Applicant's invention (dosage amounts) over a prolonged period, the basal cell carcinoma has constantly decreased in size.

[0186] With respect to Figure 7, (7a) shows mice having tumors in the skin induced in their hind legs. After continuous applications to the shaved hind legs having the tumors in the skin by rubbing in dosage amounts by Applicant's invention, the tumors have decreased in size. (See Figure 7b)

[0187] The effect of Hyaluronic acid as a drug carrier of anti-cancer agent (5-FU) 5-Fluoracil was also studied.

(Intratumour injection study)

B. EXPERIMENTAL MODEL (2)

1. Method and Material

[0188]

a. Animal : Fisher 344 rat, male 200-250g
b. Tumor model
   Fisher Bladder Carcinoma
   Tumor (2mm viable tumor fragment) was
   transplanted subcutaneously on the right
   frank by trocar
c. Treatment was started when tumor size is about
   1.5 cm.
   (2 weeks after implantation.)

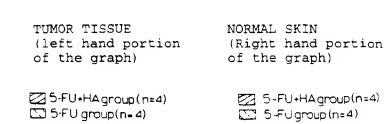
1. These drugs were administrated by intratumor injection. (right frank)
   At the same time, injection into normal skin (left frank) was carried out similarly.
   Group A : H-5-FU 5mg/kg + saline /0.3ml (i.t.) B : H-5-FU 5mg/kg + HA 15 mg/kg /0.3ml (s.c.)

3H-FU without or with HA was injected as a single dose (0.3ml) into the center of the tumor (on the right frank) with a 30 gause needle. At the same time, injection into normal skin (on the left frank) was carried out similarly.

The tumor and skin was then removed at different times (1h,6hr) for counting radioactivity of the remaining content in the tissue.

2. Result

[0189] All the results were expressed as Mean + S.E. under the following headings:



(See Figure 4' of Page 4/12)

3. Conclusion

[0190]

1. In 5-FU HA group radioactivity was accumulated and retained in the tumor tissue for a long period, whereas rapid clearance was demonstrated in normal tissue. (skin)
2. In 5-FU group, radioactivity immediately disappeared from the tumor or the normal tissue by diffusion, primarily into blood capillaries. ---- 5FU can traverse freely between the interstitial space and blood capillary.

[0191] The Effect of Hyaluronic Acid as a Drug Carrier in Target Cancer Chemotherapy

A. EXPERIMENTAL MODEL (1) Intravenous injection)

*1. **Method and Material***

[0192]

a. Animal : Fisher 344 rat, male 200-250g
b. Tumor model
Fisher Bladder Carcinoma
Tumor (2mm viable tumor fragment) was transplanted subcutaneously on the right frank by trocar
c. Treatment was started when tumor size is about
1.5 cm.(2 weeks after implantation.)....tumor weight:1.0 ± 0.3g
The drug was administered Intravenously (through the penile vein)

Group A : 5-FU 20mg/kg (3H-5-FU30μCi) + saline
B : 5-FU 20mg/kg (3H-5-FU30μCi) + HA 15mg/kg
C : 5-FU 20mg/kg (3H-5-FU30μCi) + HA 15mg/kg + (3H-HA30μCi)

2. Sample Collection

[0193] a. accumulation of ADR. 5-FU in tumor tissue and liver

(1). Tumor was surgically removed (and blood was collected) at *predeterminated time after drug administration. Tumor weight was measured (and blood was centrifuged to obtain a plasma sample.)
* 15min, 60 min, 3hr, 4hrs,.... after drug administration..... Liver was removed for radioactivity counting at the same

time.

(2). Radioactivity level in tumor tissue was counted, using a liquid scintillation counter.

3. Conclusion

Radioactivity in Tumor Tissue and Liver				
			Tumor	Liver
15min	3H-5FU	(n=6)	2810±165	18680±625
	3H-5FU+HA	(n=6)	352±190	23593±1460
	3H-5FU+3H-HA	(n=4)	4087±681	32060±2145
60min	3H-5FU	(n=3)	1751±149	5451±841
	3H-5FU+HA	(n=4)	2599±489	8265±1849
3hrs	3H-5FU	(n=6)	1493±227	2230±449
	3H-5FU+HA	(n=6)	2512±449	2897±340
	3H-5FU+3H-HA	(n=4)	3606±929	6977±1633
5hrs	3H-FU	(n=3)	853±129	1129±70
	3H-5FU+HA	(n=3)	1981±479	1754±248
	3H-5FU+3H-HA	(n=3)	2168±163	3018±325
mean± S.E. HA : 15 mg/kg (30μCi/kg) 5-FU : 20mg/kg (30μCi/kg)				

See Figure 5' of Page 5/12 of the Figures which comprises a graph entitled "RADIOACTIVITY IN TUMOR TISSUE" comparing CPM on the vertical with time in Minutes on the horizontal (for example 100, 200, 300) .

1. Radioactivity in tumor tissue in 5-FU + HA group is higher than that in 5-FU group. There is significant difference (p>0.05, ANOVA) between with and without HA at 3hrs after injection. The high intratumor concentration was retained for a prolonged time in 5-FU+HA group. (This retention was confirmed by the intratumor injection study.)
2. These results teach that HA can enhance 5-FU uptake in tumor tissue. This phenomenon results from HA distribution (in tumor tissue HA may be lost from the extracellular matrix) and the vascular uniqueness of tumor tissue (hyperpermiability of tumor vessels to macromolecular drug, HA).

As many changes can be made to the invention without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

Claims

1. The use of:

(1) a medicinal and/or therapeutic agent in a therapeutically effective amount to treat a disease or condition of the skin and/or exposed tissue and,

(2) a form of hyaluronic acid selected from hyaluronic acid and salts thereof having a molecular weight ranging from 150,000 daltons to less than 750,000 daltons for the manufacture of a pharmaceutical composition for the topical treatment of said disease or condition of the skin and/or exposed tissue, characterized in that said composition is suitable to be applied in a dosage amount in which component (2) exceeds 5 mg/cm^2 of the skin or exposed tissue to which the dosage amount is to be applied, and is in such form that component (2) is immediately available to transport component (1) percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition to be treated in the skin or exposed tissue, where the dosage amount of the composition accumulates (in the epidermis) for a prolonged period before passage therefrom, and wherein component (2) is 1 to 3 % by weight of the composition.

2. The use of Claim 1 wherein the form of hyaluronic acid is hyaluronic acid.

3. The use of Claim 1 wherein the form of hyaluronic acid is sodium hyaluronate.

4. The use of Claim 1, 2 or 3 wherein the disease and/or condition is selected from at least one of basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies and/or tumours of the skin, genital warts, cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women.

5. The use of Claim 1, 2, 3, 4 or 4 wherein the molecular weight of the form of hyaluronic acid is from 150,000 daltons to 225,000 daltons.

6. The use of Claim 1, 2, 3, 4 or 5 wherein the drug is a non-steroidal anti-inflammatory drug (NSAID).

7. The use of Claim 6 wherein the NSAID is selected from diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac.

8. The use of Claim 6 wherein the NSAID is selected from ibuprofen, piroxicam, propionic acid derivatives, acetylsalicylic acid and flunixin.

9. The use of Claim 1, 2, 3, 4 or 5 wherein the drug is an anti-cancer drug.

10. The use of Claim 9 wherein the anti-cancer drug is selected from Novantrone and 5-Fu (FLUORACIL).

11. The use of Claim 1, 2, 3, 4, 5 or 6 wherein the composition is packaged in a container from which each dosage amount is taken.

12. The use of Claim 1, 2, 3, 4, 5 or 6 wherein the composition is in a tube having a mouth of predetermined diameter from which the dosage amount of the composition is taken.

13. The use of Claim 1, 3 or 5 wherein the composition comprises in gel or cream form suitable for topical application, 3% by weight diclofenac, $2\frac{1}{2}$% by weight hyaluronic acid and/or a salt thereof, a solubilizer for solubilizing the diclofenac, and a preservative.

14. The use of Claim 13 further comprising 5% by weight glycerine and 3% benzyl alcohol.

15. The use of Claim 13 wherein the preservative is benzyl alcohol (1%) and the solubilizer is methoxypolyethylene glycol (20%).

16. The use of Claim 13, 14 or 15 further comprising a container for holding the composition.

17. The use of Claim 1, 3 or 5 wherein the composition comprises glycerine (5% by weight), benzyl alcohol (3% by weight), diclofenac sodium (3% by weight), sodium hyaluronate (2.5% by weight), and sterile water (the balance) in a container.

18. The use of Claim 1, 3 or 5 wherein the composition comprises methoxypolyethylene glycol (20% by weight), benzyl alcohol (1% by weight), diclofenac sodium (3% by weight), sodium hyaluronate (2.5% by weight), and sterile water (the balance) in a container.

19. The use of Claim 4, 5 or 6 wherein the disease and/or condition is basal cell carcinoma.

20. The use of Claim 4, 5 or 6 wherein the disease and/or condition is actinic keratosis lesions.

21. The use of Claim 4, 5 or 6 wherein the disease and/or condition is liver spots.

22. The use of Claim 4, 5 or 6 wherein the disease and/or condition is squamous cells tumours.

23. The use of Claim 4, 5 or 6 wherein the disease and/or condition is metastatic cancer of the breast to the skin.

24. The use of Claim 4, 5 or 6 wherein the disease and/or condition is metastatic melanoma in the skin.

25. The use of Claim 4, 5 or 6 wherein the disease and/or condition is malignancies and/or tumours of the skin.

26. The use of Claim 4, 5 or 6 wherein the disease and/or condition is genital warts.

27. The use of Claim 4, 5 or 6 wherein the disease and/or condition is cervical cancer.

28. The use of Claim 4, 5 or 6 wherein the disease and/or condition is HPV (Human Papilloma Virus) including HPV of the cervix.

29. The use of Claim 4, 5 or 6 wherein the disease and/or condition is psoriasis (both plaque type psoriasis and nail bed psoriasis).

30. The use of Claim 4, 5 or 6 wherein the disease and/or condition is corns on the feet.

31. The use of Claim 4, 5 or 6 wherein the disease and/or condition is hair loss on the head of pregnant women.

32. A composition comprising in a form suitable for administration to the skin and/or exposed tissue of a human, an effective amount of a non-steroidal anti-inflammatory agent (NSAID), being between 1% and 5% of the composition by weight and an amount of hyaluronic acid and/or salts thereof having a molecular weight greater than 150,000 daltons and less than 750,000 daltons and being between 1% and 3% by weight of the composition, a preservative and a solubilizer if required and water.

33. The composition of Claim 32 wherein the form of hyaluronic acid is sodium hyaluronate.

34. The composition of Claim 32 formulated in gel or cream form suitable for topical application and wherein the composition comprises 3 % by weight diclofenac, $2^1/_2$% by weight hyaluronic acid and/or a salt theroof, a solubilizer for solubilizing the diclofenac, and a preservative.

35. The composition of Claim 34 further comprising 5% by weight glycerine and 3% benzyl alcohol.

36. The composition of Claim 34 wherein the preservative is benzyl alcohol (1%) and the solubilizer is methoxypolyethylene glycol (20%).

37. The composition of Claim 34, 35 or 36 wherein the form of hyaluronic acid is in an amount suitable to provide a dosage of at least 10mg/cm^2 of skin or exposed tissue to which it is applied.

38. The composition of Claim 32 suitable for topical application comprising glycerine (5% by weight), benzyl alcohol (3 % by weight), diclofenac sodium (3% by weight), sodium hyaluronate (2.5% by weight) and sterile water (the balance) in a container.

39. The composition of Claim 32 suitable for topical application comprising methoxypolyethylene glycol (20% by weight), benzyl alcohol (1% by weight), diclofenac sodium (3 % by weight), sodium hyaluronate (2.5 % by weight), and sterile water (the balance) in a container.

40. The composition of Claim 32 suitable for topical application, comprising sterile water, glycerine, benzyl alcohol, about 1% by weight of the composition of diclofenac sodium, and about 3% by weight of the composition of sodium hyaluronate.

41. The composition of Claim 32 suitable for topical application, comprising sterile water, a solubilizer, a preservative, about 3% by weight of the composition of diclofenac sodium, and about 2.5% by weight of the composition of sodium hyaluronate.

42. The composition of Claim 32 suitable for topical application, comprising sterile water, meglumine, about 5% by weight of the composition of ibuprofen, benzyl alcohol, glycerin, and about 3 % by weight of the composition of

sodium hyaluronate.

43. The composition of Claim 32 suitable for topical application, comprising sterile water, meglumine, about 2% by weight of the composition of piroxicam, and about 2.5% by weight of the composition of sodium hyaluronate.

44. The composition of Claim 32 suitable for topical application comprising an oily phase comprising a wax and glycerin and an aqueous phase comprising: sterile water, meglumine, about 5% by weight of the composition of ibuprofen, about 1.5% by weight of the composition of sodium hyaluronate and a preservative.

45. The composition of Claim 32 suitable for topical application, comprising sterile water, preservative, about 1 % by weight of the composition of diclofenac sodium, and about 3% by weight of the composition of sodium hyaluronate.

46. The composition of Claim 32 suitable for topical application, comprising sterile water, about 2.5% by weight of the composition of sodium hyaluronate, about 1% by weight of the composition of banamine and a preservative.

47. The composition of Claim 32 suitable for topical application, comprising between about 1 to about 3% by weight of the composition of sodium hyaluronate, between about 1 to about 5% by weight of the composition of non-steroidal anti-inflammatory drug (NSAID) and the balance selected from excipients suitable for topical application and water.

48. The use according to Claim 1 wherein the composition comprises sterile water, glycerine, benzyl alcohol, about 1% by weight of the composition of diclofenac sodium, about 3% by weight of the composition of sodium hyaluronate.

49. The use according to Claim 1 wherein the composition comprises glycerine, benzyl alcohol, about 3% by weight of the composition of diclofenac sodium, about 2.5% by weight of the composition of sodium hyaluronate and sterile water.

50. The use according to Claim 1 wherein the composition comprises methoxypolyethylene glycol, benzyl alcohol, about 3% by weight of the composition of diclofenac sodium, about 2.5% by weight of the composition of sodium hyaluronate, and sterile water.

51. The use according to Claim 1 wherein the composition comprises sterile water, a solubilizer, a preservative, about 3 % by weight of the composition of diclofenac sodium, about 2.5 % by weight of the composition of sodium hyaluronate.

52. The use according to Claim 1 wherein the composition comprises sterile water, meglumine, about 5% by weight of the composition of ibuprofen, benzyl alcohol, glycerin, about 3% by weight of the composition of sodium hyaluronate.

53. The use according to Claim 1 wherein the composition comprises sterile water, meglumine, about 2% by weight of the composition of piroxicam, about 2.5% by weight of the composition of sodium hyaluronate.

54. The use according to Claim 1 wherein the composition comprises wax and glycerin and an aqueous phase comprising: sterile water, meglumine, about 5 % by weight of the composition of ibuprofen, about 1.5% by weight of the composition of sodium hyaluronate and a preservative.

55. The use according to Claim 1 wherein the composition comprises sterile water, glycerin, benzyl alcohol, about 1% by weight of the composition of diclofenac sodium, about 3% by weight of the composition of sodium hyaluronate.

56. The use according to Claim 1 wherein the composition comprises sterile water, preservative, about 1% by weight of the composition of diclofenac sodium, about 3% by weight of the composition of sodium hyaluronate.

57. The use according to Claim 1 wherein the composition comprises sterile water, about 2.5% by weight of the composition of sodium hyaluronate, about 1% by weight of the composition of Flunixin and a preservative.

58. The use according to Claim 1 wherein the composition comprises between about 1 to about 3 % by weight of the composition of sodium hyaluronic acid between about 1 to about 5 % by weight of the composition of an NSAID

and a balance selected from excipients suitable for topical application and water.

59. A pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising: 3% by weight of the composition of glycerine, 1.5% by weight of the composition of benzyl alcohol, 1% by weight of the composition of diclofenac sodium, 3% by weight of the composition of sodium hyaluronate, having a molecular weight of 661.600 daltons, 3% by weight of the composition of liquid wax and sterile water wherein the total weight of said composition is substantially 1569 g, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an amount sufficient to provide a dosage exceeding 5mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation in the epidermis before passage therefrom.

60. A pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising: 5% by weight of the composition of glycerine, 3% by weight of the composition of benzyl alcohol, 3% by weight of the composition of diclofenac sodium, 2.5% by weight of the composition of sodium hyaluronate having a molecular weight of 661,600 daltons and sterile water wherein the total weight of said composition is about 3200 g, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which sodium hyaluronate is in an amount sufficient to provide a dosage exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

61. A pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising: 20% by weight of the composition of methoxypolyethylene glycol, 1% by weight of the composition of benzyl alcohol. 3% by weight of the composition of diclofenac sodium, 2.5% by weight of the composition of sodium hyaluronate having a molecular weight of 679,000 daltons and sterile water wherein the total weight of said composition is substantially 1,597g, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an amount sufficient to provide a dosage exceeding 5mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

62. A pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising: 20% by weight of the composition of a solubilizer, methoxypolyethylene glycol, 1% by weight of the composition of a preservative, benzyl alcohol, 3% by weight of the composition of diclofenac sodium, 2.5% by weight of the composition of sodium hyaluronate having a molecular weight of 679,000 daltons, and sterile water wherein the total weight of said composition is substantially 1.597g, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an amount sufficient to provide a dosage exceeding 5mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

63. A pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising: 5.5% by weight of the composition of meglumine, 5% by weight of the composition of ibuprofen, 1% by weight of the composition of benzyl alcohol, 1 % by weight of the composition of glycerin. 3 % by weight of the composition of sodium hyaluronate having a molecular weight of 661,600 daltons, and sterile water wherein the total weight of said composition is 227g, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an amount sufficient to provide

a dosage exceeding 5mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

64. A pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising: 4% by weight of the composition of meglumine, 2% by weight of the composition of piroxicam, 2.5% by weight of the composition of sodium hyaluronate having a molecular weight of 661,600 daltons, and sterile water wherein the total weight of said composition is 217 g, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an amount sufficient to provide a dosage exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

65. A pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising: an oily phase comprising: 15% by weight of the composition of a liquid wax, 16% by weight of the composition of wax, 5 % by weight of the composition of glycerin and an aqueous phase comprising: 5% by weight of the composition of meglumine, 5% by weight of the composition of ibuprofen. 1.5% by weight of the composition of sodium hyaluronate having a molecular weight of 200,000 daltons and 0.3% by weight of the composition of a preservative, suttocide A and sterile water wherein the total weight of said composition is 3.384 g, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an amount sufficient to provide a dosage exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

66. A pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising: 3% by weight of the composition of glycerin. 1.5% by weight of the composition of benzyl alcohol, 3 % by weight of the composition of liquid wax, 1 % by weight of the composition of diclofenac sodium, 3% by weight of the composition of sodium hyaluronate having a molecular weight of 679,000 daltons, and sterile water, wherein the total weight of the said composition is 3,101g, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an amount sufficient to provide a dosage exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

67. A pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising: 1.5% by weight of the composition of a preservative, benzyl alcohol, 3% by weight of the composition of glycerin, about 1 % by weight of the composition of diclofenac sodium, 3% by weight of the composition of liquid wax, 3% by weight of the composition of sodium hyaluronate, having a molecular weight is 661,600 daltons, and sterile water wherein the total weight of said composition is about 1,569 g, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an amount sufficient to provide a dosage exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

68. A pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage

amounts can be taken for topical application comprising: an oily phase comprising 15% by weight of the composition of a liquid wax, 16% by weight of a wax and 5% by weight of the composition of glycerine and an aqueous phase comprising 5% by weight of the composition of meglumine, 1.5% by weight of the composition of sodium hyaluronate having a molecular weight 207.000 daltons, 5% by weight of the composition of ibuprofen and 0.3% by weight of the composition of a preservative, suttocide, and sterile water wherein the total weight of said composition is 3,384 g, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an amount sufficient to provide a dosage exceeding 5 mg/cm^2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

69. A pharmaceutical composition for topical application from which a substantial number of effective non-toxic dosage amounts can be taken for topical application comprising: 2.5% by weight of the composition of sodium hyaluronate having a molecular weight of 661.600 daltons, 1 % by weight of the composition of banamine, and sterile water wherein the total amount of said composition is 3.000 ml, said composition is in a dosage form suitable for topical application and said pharmaceutical composition comprises a plurality of dosage amounts each of which is in a dosage amount in which the sodium hyaluronate is in an amount sufficient to provide a dosage exceeding 5 mg/ cm2 of the skin or exposed tissue to which it is to be applied and in a form immediately available to transport the diclofenac sodium percutaneously into the epidermis of the skin or exposed tissue to the site of trauma and/or pathology of the disease or condition in the skin or exposed tissue on application to the skin and/or exposed tissue for accumulation therein in the epidermis before passage therefrom.

Patentansprüche

1. Verwendung,

(1) eines medizinischen und/oder therapeutischen Mittels zur Behandlung einer Erkrankung oder eines Zustandes der Haut und/oder eines freiliegenden Gewebes; und
(2) einer Form von Hyaluronsäure, ausgewählt aus Hyaluronsäure und Salzen davon mit einem Molekulargewicht im Bereich von 150 000 Dalton bis weniger als 750 000 Dalton, zur Herstellung einer pharmazeutischen Zusammensetzung zur örtlichen Behandlung der Erkrankung oder des Zustandes der Haut und/oder des freiliegenden Gewebes, dadurch gekennzeichnet, daß die Zusammensetzung zum Auftragen in einer Dosierungsmenge geeignet ist, in welcher die Komponente (2) mehr als 5 mg/cm^2 der Haut oder des freiliegenden Gewebes, auf welche die Dosierungsmenge aufzutragen ist, beträgt, und eine solche Form aufweist, daß die Komponente (2) sofort verfügbar ist, um die Komponente (1) perkutan in die Epidermis der Haut und/oder des freiliegenden Gewebes zu der Stelle des Traumas und/oder der Pathologie der Erkrankung oder des Zustandes, der in der Haut oder dem freiliegenden Gewebe zu behandeln ist, zu transportieren, wobei die Dosierungsmenge der Zusammensetzung sich vor ihrem Austritt über einen längeren Zeitraum (in der Epidermis) sammelt, und wobei die Komponente (2) 1 bis 3 Gew.% der Zusammensetzung beträgt.

2. Verwendung nach Anspruch 1, wobei die Form der Hyaluronsäure Hyaluronsäure ist

3. Verwendung nach Anspruch 1, wobei die Form der Hyaluronsäure Natriumhyaluronat ist.

4. Verwendung nach Anspruch 1, 2 oder 3 wobei die Erkrankung und/oder der Zustand ausgewählt ist aus mindestens einem von Basalzellenkarzinom, präkanzerösen, häufig rezidivierenden, aktinischen Keratoseläsionen, Pilzläsionen, Leberflecken, Schuppenzellentumoren, metastatischem Brustkrebs bis zur Haut, primären und metastatischen Melanomen in der Haut, Hautmalignitäten und/oder -tumoren, Genitalwarzen, Gebärmutterhalskrebs und HPV (humanes Papillomavirus) einschließlich HPV der Cervix, Psoriasis (sowohl schuppenartige Psoriasis als auch Nagelbett-Psoriasis), Hühneraugen an den Füßen und Kopfhaarausfall bei schwangeren Frauen.

5. Verwendung nach Anspruch 1, 2, 3 oder 4, wobei das Molekulargewicht der Form von Hyaluronsäure 150 000 Dalton bis 225 000 Dalton beträgt.

6. Verwendung nach Anspruch 1, 2, 3, 4 oder 5, wobei das Arzneimittel ein nicht-steroidales, antiinflammatorisch

wirkendes Medikament ("non-steroidal antiinflammatory drug" - NSAID) ist.

7. Verwendung nach Anspruch 6, wobei das NSAID ausgewählt ist aus Diclofenac, Indomethacin, Naproxen und (+/-) Tromethaminsalz von Ketorolac.

8. Verwendung nach Anspruch 6, wobei das NSAID ausgewählt ist aus Ibuprofen, Piroxicam, Propionsäurederivaten, Acetylsalicylsäure und Flunixin.

9. Verwendung nach Anspruch 1, 2, 3, 4 oder 5, wobei das Arzneimittel ein antikanzeröses Arzneimittel ist.

10. Verwendung nach Anspruch 9, wobei das Arzneimittel ausgewählt ist aus Novantron und 5-Fu (FLUOROACIL).

11. Verwendung nach Anspruch 1, 2, 3, 4, 5 oder 6, wobei die Zusammensetzung in einem Behälter verpackt ist, aus dem jede Dosierungsmenge entnommen wird.

12. Verwendung nach Anspruch 1, 2, 3, 4, 5 oder 6, wobei die Zusammensetzung in einer Tube verpackt ist, die eine Öffnung mit vorbestimmtem Durchmesser aufweist, aus welcher die Dosierungsmenge der Zusammensetzung entnommen wird.

13. Verwendung nach Anspruch 1, 3 oder 5, wobei die Zusammensetzung in zur örtlichen Anwendung geeigneter Gel- oder Cremeform, 3,5 Gew.% Diclofenac, 2,5 Gew.% Hyaluronsäure und/oder ein Salz davon, einen Löslichmacher zum Löslichmachen des Diclofenac, und ein Konservierungsmittel enthält.

14. Verwendung nach Anspruch 13, welche weiters 5 Gew.% Glycerin und 3 % Benzylalkohol aufweist.

15. Verwendung nach Anspruch 13, wobei das Konservierungsmittel Benzylalkohol (1 %) ist und der Löslichmacher Methoxypolyethylenglycol (20 %) ist.

16. Verwendung nach Anspruch 13, 14 oder 15, welche weiters einen Behälter zur Aufnahme der Zusammensetzung aufweist.

17. Verwendung nach Anspruch 1, 3 oder 5, wobei die Zusammensetzung Glycerin (5 Gew.%), Benzylalkohol (3 Gew. %), Diclofenacnatrium (3 Gew.%), Natriumhyaluronat (2,5 Gew.%) und steriles Wasser (Rest) in einem Behälter enthält.

18. Verwendung nach Anspruch 1, 3 oder 5, wobei die Zusammensetzung Methoxypolyethylenglycol (20Gew.%), Benzylalkohol (1 Gew.%), Diclofenacnatrium (3 Gew.%), Natriumhyaluronat (2,5 Gew.%) und steriles Wasser (Rest) in einem Behälter enthält.

19. Verwendung nach Anspruch 4, 5 oder 6, wobei die Erkrankung und/oder der Zustand Basalzellenkarzinom ist.

20. Verwendung nach Anspruch 4, 5 oder 6, wobei die Erkrankung und/oder der Zustand aktinische Keratoseläsionen sind.

21. Verwendung nach Anspruch 4, 5 oder 6, wobei die Erkrankung und/oder der Zustand Leberflecken sind.

22. Verwendung nach Anspruch 4, 5 oder 6, wobei die Erkrankung und/oder der Zustand Schuppenzellenturnore sind.

23. Verwendung nach Anspruch 4, 5 oder 6, wobei die Erkrankung und/oder der Zustand metastatischer Brustkrebs bis zur Haut ist.

24. Verwendung nach Anspruch 4, 5 oder 6, wobei die Erkrankung und/oder der Zustand metastatische Melanome in der Haut sind.

25. Verwendung nach Anspruch 4, 5 oder 6, wobei die Erkrankung und/oder der Zustand Hautmalignitäten und/oder -tumore sind.

26. Verwendung nach Anspruch 4, 5 oder 6, wobei die Erkrankung und/oder der Zustand Genitalwarzen sind.

27. Verwendung nach Anspruch 4, 5 oder 6, wobei die Erkrankung und/oder der Zustand Gebärmutterhalskrebs ist.

28. Verwendung nach Anspruch 4, 5 oder 6, wobei die Erkrankung und/oder der Zustand HPV (humanes Papillomavirus) einschließlich HPV der Cervix ist.

29. Verwendung nach Anspruch 4, 5 oder 6, wobei die Erkrankung und/oder der Zustand Psoriasis (sowohl schuppenartige Psoriasis als auch Nagelbettpsoriasis) ist.

30. Verwendung nach Anspruch 4, 5 oder 6, wobei die Erkrankung und/oder der Zustand Hühneraugen an den Füßen sind.

31. Verwendung nach Anspruch 4, 5 oder 6, wobei die Erkrankung und/oder der Zustand Kopfhaarausfall bei schwangeren Frauen ist.

32. Zusammensetzung, welche in zur Verabreichung an die Haut und/oder freiliegendes Gewebe eines Menschen geeignete Form, eine wirksame Menge eines nicht-steroidalen, antiinflammatorisch wirkenden Medikaments ("non-steroidal anti-inflammatory drug" - NSAID), die zwischen 1 Gew.% und 5 Gew.% der Zusammensetzung beträgt, und eine Menge an Hyaluronsäure und/oder Salzen davon mit einem Molekulargewicht von mehr als 150 000 Dalton und weniger als 750 000 Dalton, die zwischen 1 Gew.% und 3 Gew.% der Zusammensetzung beträgt, ein Konservierungsmittel und, falls erforderlich, einen Löslichmacher, und Wasser enthält.

33. Zusammensetzung nach Anspruch 32, wobei die Form der Hyaluronsäure Natriumhyaluronat ist.

34. Zusammensetzung nach Anspruch 32, formuliert in zur örtlichen Anwendung geeigneter Gel- oder Cremeform, wobei die Zusammensetzung weiters 3 Gew.% Diclofenac, 2,5 Gew.% Hyaluronsäure und/oder ein Salz davon, einen Löslichmacher zum Löslichmachen des Diclofenac und ein Konservierungsmittel enthält.

35. Zusammensetzung nach Anspruch 34, welche weiters 5 Gew.% Glycerin und 3 % Benzylalkohol enthält.

36. Zusammensetzung nach Anspruch 34, wobei das Konservierungsmittel Benzylalkohol (1 %) ist und der Löslichmacher Methoxypolyethylenglycol (20 %) ist.

37. Zusammensetzung nach Anspruch 34, 35 oder 36, wobei die Form von Hyaluronsäure in einer Menge vorliegt, die zur Bereitstellung einer Dosierung von mindestens 10 mg/cm^2 Haut oder freiliegendem Gewebe, auf welche/welches sie aufgetragen wird, geeignet ist.

38. Zusammensetzung nach Anspruch 32, die zur örtlichen Anwendung geeignet ist, und Glycerin (5 Gew.%), Benzylalkohol (3 Gew.%), Diclofenacnatrium (3 Gew.%), Natriurohyaluronat (2,5 Gew.%) und steriles Wasser (Rest) in einem Behälter enthält.

39. Zusammensetzung nach Anspruch 32, die zur örtlichen Anwendung geeignet ist und Methoxypolyethylenglycol (20 Gew.%), Benzylalkohol (1 Gevv.%), Diclofenacnatrium (3 Gew.%), Natriumhyaluronat (2,5 Gew.%) und steriles Wasser (Rest) in einem Behälter enthält.

40. Zusammensetzung nach Anspruch 32, die zur örtlichen Anwendung geeignet ist und steriles Wasser, Glycerin, Benzylalkohol, etwa 1 Gew % der Zusammensetzung Diclofenacnatrium. und etwa 3 Gew.% der Zusammensetzung Natriumhyaluronat enthält.

41. Zusammensetzung nach Anspruch 32, die zur örtlichen Anwendung geeignet ist und steriles Wasser, einen Löslichmacher, ein Konservierungsmittel, etwa 3 Gew.% der Zusammensetzung Diclofenacnatrium und etwa 2,5 Gew. % der Zusammensetzung Natriumhyaluronat enthält.

42. Zusammensetzung nach Anspruch 32, die zur örtlichen Anwendung geeignet ist und steriles Wasser, Meglumin, etwa 5 Gew.% der Zusammensetzung Ibuprofen, Benzylalkohol, Glycerin, und etwa 3 Gew.% der Zusammensetzung Natriumhyaluronat enthält.

43. Zusammensetzung nach Anspruch 32, die zur örtlichen Anwendung geeignet ist und steriles Wasser, Meglumin, etwa 2 Gew.% der Zusammensetzung Piroxicam, und etwa 2,5 Gew.% der Zusammensetzung Natriumhyaluronat

enthält.

44. Zusammensetzung nach Anspruch 32, die zur örtlichen Anwendung geeignet ist und eine ölige Phase, umfassend ein Wachs und Glycerin, und eine wäßrige Phase umfassend: steriles Wasser, Meglumin, etwa 5 Gew.% der Zusammensetzung Ibuprofen, etwa 1,5 Gew.% der Zusammensetzung Natriumhyaluronat, und ein Konservierungsmittel enthält.

45. Zusammensetzung nach Anspruch 32, die zur örtlichen Anwendung geeignet ist und steriles Wasser, Konservierungsmittel, etwa 1 Gew.% der Zusammensetzung Diclofenacnatrium, und etwa 3 Gew.% der Zusammensetzung Natriumhyaluronat enthält.

46. Zusammensetzung nach Anspruch 32, die zur örtlichen Anwendung geeignet ist und steriles Wasser, etwa 2.5 Gew.% der Zusammensetzung Natriumhyaluronat, etwa 1 Gew.% der Zusammensetzung Banamin und ein Konservierungsmittel enthält.

47. Zusammensetzung nach Anspruch 32, die zur örtlichen Anwendung geeignet ist und zwischen etwa 1 bis etwa 3 Gew.% der Zusammensetzung Natriumhyaluronat, zwischen etwa 1 bis etwa 5 Gew.% der Zusammensetzung nicht-steroidales, antiinflammatorisch wirkendes Medikament (NSAID), und den Rest, ausgewählt aus Trägersubstanzen, die zur örtlichen Anwendungen geeignet sind, und Wasser enthält.

48. Verwendung nach Anspruch 1, wobei die Zusammensetzung steriles Wasser, Glycerin, Benzylalkohol, etwa 1 Gew.% der Zusammensetzung Diclofenacnatrium, etwa 3 Gew.% der Zusammensetzung Natriumhyaluronat aufweist.

49. Verwendung nach Anspruch 1, wobei die Zusammensetzung Glycerin, Benzylalkohol, etwa 3 Gew.% der Zusammensetzung Diclofenacnatrium, etwa 2,5 Gew.% der Zusammensetzung Natriumhyaluronat und steriles Wasser aufweist.

50. Verwendung nach Anspruch 1, wobei die Zusammensetzung Methoxypolyethylenglycol, Benzylalkohol, etwa 3 Gew.% der Zusammensetzung Diclofenacnatrium, etwa 2.5 Gew.% der Zusammensetzung Natriumhyaluronat und steriles Wasser enthält.

51. Verwendung nach Anspruch 1, wobei die Zusammensetzung steriles Wasser, einen Löslichmacher, ein Konservierungsmittel, etwa 3 Gew.% der Zusammensetzung Diclofenacnatrium, etwa 2.5 Gew.% der Zusammensetzung Natriumhyaluronat enthält.

52. Verwendung nach Anspruch 1, wobei die Zusammensetzung steriles Wasser, Meglumin, etwa 5 Gew.% der Zusammensetzung Ibuprofen, Benzylalkohol, Glycerin, etwa 3 Gew.% der Zusammensetzung Natriumhyaluronat enthält.

53. Verwendung nach Anspruch 1, wobei die Zusammensetzung steriles Wasser, Meglumin, etwa 2 Gew.% der Zusammensetzung Piroxicam, etwa 2,5 Gew.% der Zusammensetzung Natriumhyaluronat enthält.

54. Verwendung nach Anspruch 1, wobei die Zusammensetzung Wachs und Glycerin und eine wäßrige Phase, die steriles Wasser, Meglumin, etwa 5 Gew.% der Zusammensetzung Ibuprofen, etwa 1,5 Gew.% der Zusammensetzung Natriumhyaluronat und ein Konservierungsmittel enthält, aufweist.

55. Verwendung nach Anspruch 1, wobei die Zusammensetzung steriles Wasser, Glycerin, Benzylalkohol, etwa 1 Gew.% der Zusammensetzung Diclofenacnatrium, etwa 3 Gew.% der Zusammensetzung Natriumhyaluronat enthält.

56. Verwendung nach Anspruch 1, wobei die Zusammensetzung steriles Wasser, Konservierungsmittel, etwa 1 Gew.% der Zusammensetzung Diclofenacnatrium, etwa 3 Gew.% der Zusammensetzung Natriumhyaluronat enthält.

57. Verwendung nach Anspruch 1, wobei die Zusammensetzung steriles Wasser, etwa 2,5 Gew.% der Zusammensetzung Natriumhyaluronat, etwa 1 Gew.% der Zusammensetzung Flunixin und ein Konservierungsmittel enthält.

58. Verwendung nach Anspruch 1, wobei die Zusammensetzung zwischen etwa 1 bis etwa 3 Gew.% der Zusammen-

setzung Natriumhyaluronat, zwischen etwa 1 bis etwa 5 Gew.% der Zusammensetzung eines NSAID, und einen Rest, ausgewählt aus Trägersubstanzen, die zur örtlichen Anwendungen geeignet sind, und Wasser, enthält.

59. Pharmazeutische Zusammensetzung zur örtlichen Anwendung, von welcher eine wesentliche Anzahl wirksamer, nicht-toxischer Dosierungsmengen zur örtlichen Anwendung entnommen werden können, umfassend: 3 Gew.% der Zusammensetzung Glycerin, 1,5 Gew.% der Zusammensetzung Benzylalkohol, 1 Gew.% der Zusammensetzung Diclofenacnatrium, 3 Gew.% der Zusammensetzung Natriumhyaluronat mit einem Molekulargewicht von 661 600 Dalton, 3 Gew.% der Zusammensetzung Flüssigwachs und steriles Wasser, wobei das Gesamtgewicht der Zusammensetzung im wesentlichen 1569 g beträgt, wobei die Zusammensetzung in einer Dosierungsform vorliegt, die zur örtlichen Anwendung geeignet ist, und die pharmazeutische Zusammensetzung eine Mehrzahl von Dosierungsmengen umfaßt, von welchen jede eine Dosierungsmenge ist, bei welcher das Natriumhyaluronat in einer Menge vorliegt, die ausreichend ist für die Bereitstellung einer Dosierung von mehr als 5 mg/cm^2 der Haut oder des freiliegenden Gewebes, auf welche/ welches sie aufgetragen wird, sowie in einer sofort verfügbaren Form vorliegt, um das Diclofenacnatrium perkutan in die Epidermis der Haut oder des freiliegenden Gewebes zu der Stelle des Traumas und/oder der Pathologie der Erkrankung oder des Zustandes in der Haut oder dem freiliegenden Gewebe zu transportieren, wenn sie auf die Haut und/oder das freiliegende Gewebe aufgetragen wird, um sich in der Epidermis vor dem Übertritt aus dieser anzusammeln.

60. Pharmazeutische Zusammensetzung zur örtlichen Anwendung, von welcher eine wesentliche Anzahl wirksamer, nicht-toxischer Dosierungsmengen zur örtlichen Anwendung entnommen werden können, umfassend: 5 Gew.% der Zusammensetzung Glycerin, 3 Gew.% der Zusammensetzung Benzylalkohol, 3 Gew.% der Zusammensetzung Diclofenacnatrium, 2,5 Gew.% der Zusammensetzung Natriumhyaluronat mit einem Molekulargewicht von 661 600 Dalton, und steriles Wasser, wobei das Gesamtgewicht der Zusammensetzung etwa 3200 g beträgt, wobei die Zusammensetzung in einer Dosierungsform vorliegt, die zur örtlichen Anwendung geeignet ist, und die pharmazeutische Zusammensetzung eine Mehrzahl von Dosierungsmengen umfaßt, von welchen jede eine Dosierungsmenge ist, bei welcher das Natriumhyaluronat in einer Menge vorliegt, die ausreichend ist für die Bereitstellung einer Dosierung von mehr als 5 mg/cm^2 der Haut oder des freiliegenden Gewebes, auf welche/welches sie aufgetragen wird, sowie in einer sofort verfügbaren Form vorliegt, um das Diclofenacnatrium perkutan in die Epidermis der Haut oder des freiliegenden Gewebes zu der Stelle des Traumas und/oder der Pathologie der Erkrankung oder des Zustandes in der Haut oder dem freiliegenden Gewebe zu transportieren, wenn sie auf die Haut und/ oder das freiliegende Gewebe aufgetragen wird, um sich in der Epidermis vor dem Übertritt aus dieser anzusammeln.

61. Pharmazeutische Zusammensetzung zur örtlichen Anwendung, von welcher eine wesentliche Anzahl wirksamer, nicht-toxischer Dosierungsmengen zur örtlichen Anwendung entnommen werden können, umfassend: 20 Gew.% der Zusammensetzung Methoxypolyethylenglycol, 1 Gew.% der Zusammensetzung Benzylalkohol, 3 Gew.% der Zusammensetzung Diclofenacnatrium, 2,5 Gew.% der Zusammensetzung Natriumhyaluronat mit einem Molekulargewicht von 679 000 Dalton, und steriles Wasser, wobei das Gesamtgewicht der Zusammensetzung im wesentlichen 1597 g beträgt, wobei die Zusammensetzung in einer Dosierungsform vorliegt, die zur örtlichen Anwendung geeignet ist, und die pharmazeutische Zusammensetzung eine Mehrzahl von Dosierungsmengen umfaßt, von welchen jede eine Dosierungsmenge ist, bei welcher das Natriumhyaluronat in einer Menge vorliegt, die ausreichend ist für die Bereitstellung einer Dosierung von mehr als 5 mg/cm^2 der Haut oder des freiliegenden Gewebes, auf welche/welches sie aufgetragen wird, sowie in einer sofort verfügbaren Form vorliegt, um das Diclofenacnatrium perkutan in die Epidermis der Haut oder des freiliegenden Gewebes zu der Stelle des Traumas und/oder der Pathologie der Erkrankung oder des Zustandes in der Haut oder dem freiliegenden Gewebe zu transportieren, wenn sie auf die Haut und/oder das freiliegende Gewebe aufgetragen wird, um sich in der Epidermis vor dem Übertritt aus dieser anzusammeln.

62. Pharmazeutische Zusammensetzung zur örtlichen Anwendung, von welcher eine wesentliche Anzahl wirksamer, nicht-toxischer Dosierungsmengen zur örtlichen Anwendung entnommen werden können, umfassend: 20 Gew.% der Zusammensetzung eines Löslichmachers, Methoxypolyethylenglycol, 1 Gew.% der Zusammensetzung eines Konservierungsmittels, Benzylalkohol, 3 Gew.% der Zusammensetzung Diclofenacnatrium, 2,5 Gew.% der Zusammensetzung Natriumhyaluronat mit einem Molekulargewicht von 679 000 Dalton, und steriles Wasser, wobei das Gesamtgewicht der Zusammensetzung im wesentlichen 1597 g beträgt, wobei die Zusammensetzung in einer Dosierungsform vorliegt, die zur örtlichen Anwendung geeignet ist, und die pharmazeutische Zusammensetzung eine Mehrzahl von Dosierungsmengen umfaßt, von welchen jede eine Dosierungsmenge ist, bei welcher das Natriumhyaluronat in einer Menge vorliegt, die ausreichend ist für die Bereitstellung einer Dosierung von mehr als 5 mg/cm^2 der Haut oder des freiliegenden Gewebes, auf welche/welches sie aufgetragen wird, sowie in einer

sofort verfügbaren Form vorliegt, um das Diclofenacnatrium perkutan in die Epidermis der Haut oder des freiliegenden Gewebes zu der Stelle des Traumas und/oder der Pathologie der Erkrankung oder des Zustandes in der Haut oder dem freiliegenden Gewebe zu transportieren, wenn sie auf die Haut und/oder das freiliegende Gewebe aufgetragen wird, um sich in der Epidermis vor dem Übertritt aus dieser anzusammeln.

63. Pharmazeutische Zusammensetzung zur örtlichen Anwendung, von welcher eine wesentliche Anzahl wirksamer, nicht-toxischer Dosierungsmengen zur örtlichen Anwendung entnommen werden können, umfassend: 5,5. Gew.% der Zusammensetzung Meglumin, 5 Gew.% der Zusammensetzung Ibuprofen, 1 Gew.% der Zusammensetzung Benzylalkohol, 1 Gew.% der Zusammensetzung Glycerin, 3 Gew.% der Zusammensetzung Natriumhyaluronat mit einem Molekulargewicht von 661 600 Dalton, und steriles Wasser, wobei das Gesamtgewicht der Zusammensetzung 227 g beträgt, wobei die Zusammensetzung in einer Dosierungsform vorliegt, die zur örtlichen Anwendung geeignet ist, und die pharmazeutische Zusammensetzung eine Mehrzahl von Dosierungsmengen umfaßt, von welchen jede eine Dosierungsmenge ist, bei welcher das Natriumhyaluronat in einer Menge vorliegt, die ausreichend ist für die Bereitstellung einer Dosierung von mehr als 5 mg/cm^2 der Haut oder des freiliegenden Gewebes, auf welche/welches sie aufgetragen wird, sowie in einer sofort verfügbaren Form vorliegt, um das Diclofenacnatrium perkutan in die Epidermis der Haut oder des freiliegenden Gewebes zu der Stelle des Traumas und/oder der Pathologie der Erkrankung oder des Zustandes in der Haut oder dem freiliegenden Gewebe zu transportieren, wenn sie auf die Haut und/oder das freiliegende Gewebe aufgetragen wird, um sich in der Epidermis vor dem Übertritt aus dieser anzusammeln.

64. Pharmazeutische Zusammensetzung zur örtlichen Anwendung, von welcher eine wesentliche Anzahl wirksamer, nicht-toxischer Dosierungsmengen zur örtlichen Anwendung entnommen werden können, umfassend: 4 Gew.% der Zusammensetzung Meglumin, 2 Gew.% der Zusammensetzung Piroxicam, 2,5 Gew.% der Zusammensetzung Natriumhyaluronat mit einem Molekulargewicht von 661 600 Dalton, und steriles Wasser, wobei das Gesamtgewicht der Zusammensetzung 217 g beträgt, wobei die Zusammensetzung in einer Dosierungsform vorliegt, die zur örtlichen Anwendung geeignet ist, und die pharmazeutische Zusammensetzung eine Mehrzahl von Dosierungsmengen umfaßt, von welchen jede eine Dosierungsmenge ist, bei welcher das Natriumhyaluronat in einer Menge vorliegt, die ausreichend ist für die Bereitstellung einer Dosierung von mehr als 5 mg/cm^2 der Haut oder des freiliegenden Gewebes, auf welche/welches sie aufgetragen wird, sowie in einer sofort verfügbaren Form vorliegt, um das Diclofenacnatrium perkutan in die Epidermis der Haut oder des freiliegenden Gewebes zu der Stelle des Traumas und/oder der Pathologie der Erkrankung oder des Zustandes in der Haut oder dem freiliegenden Gewebe zu transportieren, wenn sie auf die Haut und/oder das freiliegende Gewebe aufgetragen wird, um sich in der Epidermis vor dem Übertritt aus dieser anzusammeln.

65. Pharmazeutische Zusammensetzung zur örtlichen Anwendung, von welcher eine wesentliche Anzahl wirksamer, nicht-toxischer Dosierungsmengen zur örtlichen Anwendung entnommen werden können, umfassend: eine ölige Phase, umfassend: 15 Gew.% der Zusammensetzung Flüssigwachs, 16 Gew.% der Zusammensetzung Wachs, 5 Gew.% der Zusammensetzung Glycerin, und eine wäßrige Phase, umfassend: 5 Gew.% der Zusammensetzung Meglumin, 5 Gew.% der Zusammensetzung Ibuprofen, 1,5 Gew.% der Zusammensetzung Natriumhyaluronat mit einem Molekulargewicht von 200 000 Dalton, und 0,3 Gew.% der Zusammensetzung eines Konservierungsmittels, Suttocid A, und steriles Wasser, wobei das Gesamtgewicht der Zusammensetzung 3384 g beträgt, wobei die Zusammensetzung in einer Dosierungsform vorliegt, die zur örtlichen Anwendung geeignet ist, und die pharmazeutische Zusammensetzung eine Mehrzahl von Dosierungsmengen umfaßt, von welchen jede eine Dosierungsmenge ist, bei welcher das Natriumhyaluronat in einer Menge vorliegt, die ausreichend ist für die Bereitstellung einer Dosierung von mehr als 5 mg/cm^2 der Haut oder des freiliegenden Gewebes, auf welche/welches sie aufgetragen wird, sowie in einer sofort verfügbaren Form vorliegt, um das Diclofenacnatrium perkutan in die Epidermis der Haut oder des freiliegenden Gewebes zu der Stelle des Traumas und/oder der Pathologie der Erkrankung oder des Zustandes in der Haut oder dem freiliegenden Gewebe zu transportieren, wenn sie auf die Haut und/oder das freiliegende Gewebe aufgetragen wird, um sich in der Epidermis vor dem Übertritt aus dieser anzusammeln.

66. Pharmazeutische Zusammensetzung zur örtlichen Anwendung, von welcher eine wesentliche Anzahl wirksamer, nicht-toxischer Dosierungsmengen zur örtlichen Anwendung entnommen werden können, umfassend: 3 Gew.% der Zusammensetzung Glycerin, 1,5 Gew.% der Zusammensetzung Benzylalkohol, 3 Gew.% der Zusammensetzung Flüssigwachs, 1 Gew.% der Zusammensetzung Diclofenacnatrium, 3 Gew.% der Zusammensetzung Natriumhyaluronat mit einem Molekulargewicht von 679 000 Dalton, und steriles Wasser, wobei das Gesamtgewicht der Zusammensetzung etwa 3101 g beträgt, wobei die Zusammensetzung in einer Dosierungsform vorliegt, die zur örtlichen Anwendung geeignet ist, und die pharmazeutische Zusammensetzung eine Mehrzahl von Dosie-

rungsmengen umfaßt, von welchen jede eine Dosierungsmenge ist, bei welcher das Natriumhyaluronat in einer Menge vorliegt, die ausreichend ist für die Bereitstellung einer Dosierung von mehr als 5 mg/cm^2 der Haut oder des freiliegenden Gewebes, auf welche/welches sie aufgetragen wird, sowie in einer sofort verfügbaren Form vorliegt, um das Diclofenacnatrium perkutan in die Epidermis der Haut oder des freiliegenden Gewebes zu der Stelle des Traumas und/oder der Pathologie der Erkrankung oder des Zustandes in der Haut oder dem freiliegenden Gewebe zu transportieren, wenn sie auf die Haut und/oder das freiliegende Gewebe aufgetragen wird, um sich in der Epidermis vor dem Übertritt aus dieser anzusammeln.

67. Pharmazeutische Zusammensetzung zur örtlichen Anwendung, von welcher eine wesentliche Anzahl wirksamer, nicht-toxischer Dosierungsmengen zur örtlichen Anwendung entnommen werden können, umfassend: 1.5 Gew. % der Zusammensetzung eines Konservierungsmittels, Benzylalkohol, 3 Gew.% der Zusammensetzung Glycerin, etwa 1 Gew.% der Zusammensetzung Diclofenacnatrium, 3 Gew.% der Zusammensetzung Flüssigwachs, 3 Gew. % der Zusammensetzung Natriumhyaluronat mit einem Molekulargewicht von 661 600 Dalton, und steriles Wasser, wobei das Gesamtgewicht der Zusammensetzung etwa 1569 g beträgt, wobei die Zusammensetzung in einer Dosierungsform vorliegt, die zur örtlichen Anwendung geeignet ist, und die pharmazeutische Zusammensetzung eine Mehrzahl von Dosierungsmengen umfaßt, von welchen jede eine Dosierungsmenge ist, bei welcher das Natriumhyaluronat in einer Menge vorliegt, die ausreichend ist für die Bereitstellung einer Dosierung von mehr als 5 mg/cm^2 der Haut oder des freiliegenden Gewebes, auf welche/welches sie aufgetragen wird, sowie in einer sofort verfügbaren Form vorliegt, um das Diclofenacnatrium perkutan in die Epidermis der Haut oder des freiliegenden Gewebes zu der Stelle des Traumas und/oder der Pathologie der Erkrankung oder des Zustandes in der Haut oder dem freiliegenden Gewebe zu transportieren, wenn sie auf die Haut und/ oder das freiliegende Gewebe aufgetragen wird, um sich in der Epidermis vor dem Übertritt aus dieser anzusammeln.

68. Pharmazeutische Zusammensetzung zur örtlichen Anwendung, von welcher eine wesentliche Anzahl wirksamer, nicht-toxischer Dosierungsmengen zur örtlichen Anwendung entnommen werden können, umfassend: eine ölige Phase, umfassend: 15 Gew.% der Zusammensetzung Flüssigwachs, 16 Gew.% der Zusammensetzung Wachs, 5 Gew.% der Zusammensetzung Glycerin, und eine wäßrige Phase, umfassend: 5 Gew.% der Zusammensetzung Meglurnin, 1,5 Gew.% der Zusammensetzung Natriumhyaluronat mit einem Molekulargewicht von 207 000 Dalton, 5 Gew.% der Zusammensetzung Ibuprofen, und 0,3 Gew.% der Zusammensetzung eines Konservierungsmittels, Suttocid, und steriles Wasser, wobei das Gesamtgewicht der Zusammensetzung 3384 g beträgt, wobei die Zusammensetzung in einer Dosierungsform vorliegt, die zur örtlichen Anwendung geeignet ist, und die pharmazeutische Zusammensetzung eine Mehrzahl von Dosierungsmengen umfaßt, von welchen jede eine Dosierungsmenge ist, bei welcher das Natriumhyaluronat in einer Menge vorliegt, die ausreichend ist für die Bereitstellung einer Dosierung von mehr als 5 mg/cm^2 der Haut oder des freiliegenden Gewebes, auf welche/welches sie aufgetragen wird, sowie in einer sofort verfügbaren Form vorliegt, um das Diclofenacnatrium perkutan in die Epidermis der Haut oder des freiliegenden Gewebes zu der Stelle des Traumas und/oder der Pathologie der Erkrankung oder des Zustandes in der Haut oder dem freiliegenden Gewebe zu transportieren, wenn sie auf die Haut und/oder das freiliegende Gewebe aufgetragen Wird, um sich in der Epidermis vor dem Übertritt aus dieser anzusammeln.

69. Pharmazeutische Zusammensetzung zur örtlichen Anwendung, von welcher eine wesentliche Anzahl wirksamer, nicht-toxischer Dosierungsmengen zur örtlichen Anwendung entnommen werden können, umfassend: 2.5 Gew. % der Zusamanensetzung Natriumhyaluronat mit einem Molekulargewicht von 661 600 Dalton, 1 Gew.% der Zusammensetzung Banamin, und steriles Wasser, wobei die Gesamtmenge der Zusammensetzung 3000 ml beträgt, wobei die Zusammensetzung in einer Dosierungsform vorliegt, die zur örtlichen Anwendung geeignet ist, und die pharmazeutische Zusammensetzung eine Mehrzahl von Dosierungsmengen umfaßt, von welchen jede eine Dosierungsmenge ist, bei welcher das Natriumhyaluronat in einer Menge vorliegt, die ausreichend ist für die Bereitstellung einer Dosierung von mehr als 5 mg/cm^2 der Haut oder des freiliegenden Gewebes, auf welche/welches sie aufgetragen wird, sowie in einer sofort verfügbaren Form vorliegt, um das Diclofenacnatrium perkutan in die Epidermis der Haut oder des freiliegenden Gewebes zu der Stelle des Traumas und/oder der Pathologie der Erkrankung oder des Zustandes in der Haut oder dem freiliegenden Gewebe zu transportieren, wenn sie auf die Haut und/ oder das freiliegende Gewebe aufgetragen wird, um sich in der Epidermis vor dem Übertritt aus dieser anzusammeln.

Revendications

1. Utilisation de :

(1) un agent médicinal et/ou thérapeutique dans une quantité thérapeutiquement efficace pour traiter une maladie ou affection de la peau et/ou tissu exposé et ;
(2) une forme de l'acide hyaluronique choisie parmi l'acide hyaluronique et les sels de celui-ci ayant un poids moléculaire allant de 150 000 daltons à moins de 750 000 daltons pour la fabrication d'une composition pharmaceutique pour le traitement topique de ladite maladie ou affection de la peau et/ou tissu exposé,
caractérisée en ce que ladite composition est appropriée pour être appliquée dans une quantité, dosée dans laquelle le composant (2) dépasse 5 mg/cm^2 de la peau ou tissu exposé auquel la quantité dosée doit être appliquée, et est dans une forme telle que le composant (2) est immédiatement disponible pour le transport du composant (1) par voie percutanée dans l'épiderme de la peau ou tissu exposé au site de la lésion et/ou pathologie de la maladie ou affection à traiter dans la peau ou tissu exposé, où la quantité dosée de la composition s'accumule (dans l'épiderme) pendant une période prolongée avant passage à partir de là et dans laquelle le composant (2) est de 1 à 3% en poids de la composition.

2. Utilisation selon la revendication 1, dans laquelle la forme de l'acide hyaluronique est l'acide hyaluronique.

3. Utilisation selon la revendication 1, dans laquelle la forme de l'acide hyaluronique est l'hyaluronate de sodium.

4. Utilisation selon la revendication 1, 2 ou 3, dans laquelle la maladie et/ou affection est choisie parmi au moins une des suivantes : le carcinome des cellules basales, les lésions de kératoses actiniques précancéreuses, souvent récurrentes, les lésions fongiques, les taches hépatiques, les tumeurs des cellules de l'épithélium malpighien, le cancer métastatique du sein au niveau de la peau, le mélanome primaire et métastatique dans la peau, les tumeurs malignes et/ou les tumeurs de la peau, les verrues génitales, le cancer cervical et le HPV (virus du papillome humain) incluant le HPV du col, le psoriasis (à la fois le psoriasis de type plaque et le psoriasis du lit unguéal), les cors sur le pied et la perte des cheveux sur la tête de la femme enceinte.

5. Utilisation selon la revendication 1, 2, 3 ou 4 dans laquelle le poids moléculaire de la forme de l'acide hyaluronique est de 150 000 daltons à 225 000 daltons.

6. Utilisation selon la revendication 1, 2, 3, 4 ou 5 dans laquelle le médicament est un médicament anti-inflammatoire non stéroïdien (NSAID).

7. Utilisation selon la revendication 6, dans laquelle le NSAID est choisi parmi le diclofénac, l'indométacine, le naproxène et le sel de trométhamine (+/-) de kétorolac.

8. Utilisation selon la revendication 6, dans laquelle le NSAID est choisi parmi l'ibuprofène, le piroxicam, les dérivés de l'acide propionique, l'acide acétylsalicylique et la flunixine.

9. Utilisation selon la revendication 1, 2, 3, 4, ou 5 dans laquelle le médicament est un médicament anticancéreux.

10. Utilisation selon la revendication 9, dans laquelle le médicament anticancéreux est choisi parmi la Novantrone et le 5-Fu (FLUORACIL).

11. Utilisation selon la revendication 1, 2, 3, 4, 5 ou 6 dans laquelle la composition est emballée dans un conteneur à partir duquel chaque quantité dosée est prise.

12. Utilisation selon la revendication 1, 2, 3, 4, 5 ou 6 dans laquelle la composition est dans un tube ayant une ouverture de diamètre prédéterminé à partir duquel la quantité dosée de la composition est prise.

13. Utilisation selon la revendication 1, 3 ou 5 dans laquelle la composition comprend dans une forme de gel ou de crème appropriée pour l'application topique, 3% en poids de diclofénac, 2 %% en poids d'acide hyaluronique et/ou un sel de celui-ci, un solubilisant pour solubiliser le diclofénac et un conservateur.

14. Utilisation selon la revendication 13, comprenant en outre 5% en poids de glycérine et 3% d'alcool benzylique.

15. Utilisation selon la revendication 13, dans laquelle le conservateur est l'alcool benzylique (1%) et le solubilisant est le méthoxypolyéthylèneglycol (20%).

16. Utilisation selon la revendication 13, 14 ou 15 comprenant en outre un conteneur pour maintenir la composition.

17. Utilisation selon la revendication 1, 3 ou 5 dans laquelle la composition comprend de la glycérine (5% en poids), de l'alcool benzylique (3% en poids), du diclofénac sodique (3% en poids), de l'hyaluronate de sodium (2,5% en poids) et de l'eau stérile (la balance) dans un conteneur.

18. Utilisation selon la revendication 1, 3 ou 5 dans laquelle la composition comprend du méthoxypolyéthylèneglycol (20% en poids), de l'alcool benzylique (1% en poids), du diclofénac sodique (3% en poids), de l'hyaluronate de sodium (2,5% en poids) et de l'eau stérile (la balance) dans un conteneur.

19. Utilisation selon la revendication 4, 5 ou 6 dans laquelle la maladie et/ou affection est le carcinome des cellules basales.

20. Utilisation selon la revendication 4, 5 ou 6 dans laquelle la maladie et/ou affection consiste en lésions de kératoses actiniques.

21. Utilisation selon la revendication 4, 5 ou 6 dans laquelle la maladie et/ou affection sont les taches hépatiques.

22. Utilisation selon la revendication 4, 5 ou 6 dans laquelle la maladie et/ou affection consiste en tumeurs des cellules de l'épithélium malpighien.

23. Utilisation selon la revendication 4, 5 ou 6 dans laquelle la maladie et/ou affection est le cancer métastatique du sein au niveau de la peau.

24. Utilisation selon la revendication 4, 5 ou 6 dans laquelle la maladie et/ou affection est le mélanome métastatique dans la peau.

25. Utilisation selon la revendication 4, 5 ou 6 dans laquelle la maladie et/ou affection consiste en tumeurs malignes et/ou tumeurs de la peau.

26. Utilisation selon la revendication 4, 5 ou 6 dans laquelle la maladie et/ou affection consiste en verrues génitales.

27. Utilisation selon la revendication 4, 5 ou 6 dans laquelle la maladie et/ou affection est le cancer cervical.

28. Utilisation selon la revendication 4, 5 ou 6 dans laquelle la maladie et/ou affection est le HPV (virus du papillome humain) incluant le HPV du col.

29. Utilisation selon la revendication 4, 5 ou 6 dans laquelle la maladie et/ou affection est le psoriasis (à la fois le psoriasis de type plaque et le psoriasis du lit unguéal)

30. Utilisation selon la revendication 4, 5 ou 6 dans laquelle la maladie et/ou affection consiste en cors sur le pied.

31. Utilisation selon la revendication 4, 5 ou 6 dans laquelle la maladie et/ou affection est la perte des cheveux sur la tête de la femme enceinte.

32. Composition comprenant dans une forme appropriée pour l'administration à la peau et/ou tissu exposé d'un être humain, une quantité efficace d'un agent anti-inflammatoire non stéroïdien (NSAID), étant entre 1% et 5% de la composition en poids et une quantité d'acide hyaluronique et/ou sels de celui-ci ayant un poids moléculaire supérieur à 150 000 daltons et inférieur à 750 000 daltons et étant entre 1% et 3% en poids de la composition, un conservateur et un solubilisant si requis et de l'eau.

33. Composition selon la revendication 32 dans laquelle la forme de l'acide hyaluronique est l'hyaluronate de sodium.

34. Composition selon la revendication 32 formulée sous forme de gel ou crème appropriée pour l'application topique et dans laquelle la composition comprend 3% en poids de diclofénac, 2 ½% en poids d'acide hyaluronique et/ou un sel de celui-ci, un solubilisant pour solubiliser le diclofénac et un conservateur.

35. Composition selon la revendication 34, comprenant en outre 5% en poids de glycérine et 3% d'alcool benzylique.

36. Composition selon la revendication 34, dans laquelle le conservateur est l'alcool benzylique (1%) et le solubilisant

est le méthoxypolyéthylèneglycol (20%).

37. Composition selon la revendication 34, 35 ou 36 dans laquelle la forme de l'acide hyaluronique est dans une quantité appropriée pour fournir un dosage d'au moins 10 mg/cm^2 de peau ou tissu exposé auquel elle est appliquée.

38. Composition selon la revendication 32 appropriée pour l'application topique, comprenant de la glycérine (5% en poids), de l'alcool benzylique (3% en poids), du diclofénac sodique (3% en poids), de l'hyaluronate de sodium (2,5% en poids) et de l'eau stérile (la balance) dans un conteneur.

39. Composition selon la revendication 32 appropriée pour l'application topique, comprenant du méthoxy-polyéthylèneglycol (20% en poids), de l'alcool benzylique (1% en poids), du diclofénac sodique (3% en poids), de l'hyaluronate de sodium (2,5% en poids) et de l'eau stérile (la balance) dans un conteneur.

40. Composition selon la revendication 32 appropriée pour l'application topique, comprenant de l'eau stérile, de la glycérine, de l'alcool benzylique, environ 1% en poids de la composition de diclofénac sodique et environ 3% en poids de la composition d'hyaluronate de sodium.

41. Composition selon la revendication 32 appropriée pour l'application topique, comprenant de l'eau stérile, un solubilisant, un conservateur, environ 3% en poids de la composition de diclofénac sodique et environ 2,5% en poids de la composition d'hyaluronate de sodium.

42. Composition selon la revendication 32 appropriée pour l'application topique, comprenant de l'eau stérile, de la méglumine, environ 5% en poids de la composition d'ibuprofène, d'alcool benzylique, de glycérine, et environ 3% en poids de la composition d'hyaluronate de sodium.

43. Composition selon la revendication 32 appropriée pour l'application topique, comprenant de l'eau stérile, de la méglumine, environ 2% en poids de la composition de piroxicam et environ 2,5% en poids de la composition d'hyaluronate de sodium.

44. Composition selon la revendication 32 appropriée pour l'application topique, comprenant une phase huileuse comprenant une cire et de la glycérine et une phase aqueuse comprenant : de l'eau stérile, de la méglumine, environ 5% en poids de la composition d'ibuprofène, environ 1,5% en poids de la composition d'hyaluronate de sodium et un conservateur.

45. Composition selon la revendication 32 appropriée pour l'application topique, comprenant de l'eau stérile, un conservateur, environ 1% en poids de la composition de diclofénac sodique et environ 3% en poids de la composition d'hyaluronate de sodium.

46. Composition selon la revendication 32 appropriée pour l'application topique, comprenant de l'eau stérile, environ 2,5% en poids de la composition d'hyaluronate de sodium, environ 1% en poids de la composition de banamine et un conservateur.

47. Composition selon la revendication 32 appropriée pour l'application topique, comprenant entre environ 1 à environ 3% en poids de la composition d'hyaluronate de sodium, entre environ 1 à environ 5% en poids de la composition de médicament anti-inflammatoire non stéroïdien (NSAID) et la balance choisie parmi les excipients appropriés pour l'application topique et de l'eau.

48. Utilisation selon la revendication 1 dans laquelle la composition comprend de l'eau stérile, de la glycérine, de l'alcool benzylique, environ 1% en poids de la composition de diclofénac sodique, environ 3% en poids de la composition d'hyaluronate de sodium.

49. Utilisation selon la revendication 1 dans laquelle la composition comprend de la glycérine, de l'alcool benzylique, environ 3% en poids de la composition de diclofénac sodique, environ 2,5% en poids de la composition d'hyaluronate de sodium et de l'eau stérile.

50. Utilisation selon la revendication 1 dans laquelle la composition comprend du méthoxy-polyéthylèneglycol, de l'alcool benzylique, environ 3% en poids de la composition de diclofénac sodique, environ 2,5% en poids de la

composition d'hyaluronate de sodium et de l'eau stérile.

51. Utilisation selon la revendication 1 dans laquelle la composition comprend de l'eau stérile, un solubilisant, un conservateur, environ 3% en poids de la composition de diclofénac sodique, environ 2,5% en poids de la composition d'hyaluronate de sodium.

52. Utilisation selon la revendication 1 dans laquelle la composition comprend de l'eau stérile, de la méglumine, environ 5% en poids de la composition d'ibuprofène, d'alcool benzylique, de glycérine, environ 3% en poids de la composition d'hyaluronate de sodium.

53. Utilisation selon la revendication 1 dans laquelle la composition comprend de l'eau stérile, de la méglumine, environ 2% en poids de la composition de piroxicam. environ 2,5% en poids de la composition d'hyaluronate de sodium.

54. Utilisation selon la revendication 1 dans laquelle la composition comprend de la cire et de la glycérine et une phase aqueuse comprenant : de l'eau stérile, de la méglumine, environ 5% en poids de la composition d'ibuprofène, environ 1,5% en poids de la composition d'hyaluronate de sodium et un conservateur.

55. Utilisation selon la revendication 1 dans laquelle la composition comprend de l'eau stérile, de la glycérine, de l'alcool benzylique, environ 1% en poids de la composition de diclofénac sodique, environ 3% en poids de la composition d'hyaluronate de sodium.

56. Utilisation selon la revendication 1 dans laquelle la composition comprend de l'eau stérile, un conservateur, environ 1% en poids de la composition de diclofénac sodique, environ 3% en poids de la composition d'hyaluronate de sodium.

57. Utilisation selon la revendication 1 dans laquelle la composition comprend de l'eau stérile, environ 2,5% en poids de la composition d'hyaluronate de sodium, environ 1% en poids de la composition de flunixine et un conservateur.

58. Utilisation selon la revendication 1 dans laquelle la composition comprend entre environ 1 à environ 3% en poids de la composition d'hyaluronate de sodium, entre environ 1 à environ 5% en poids de la composition d'un NSAID et une balance choisie parmi les excipients appropriés pour l'application topique et de l'eau.

59. Composition pharmaceutique pour l'application topique à partir de laquelle un nombre substantiel de quantités dosées non toxiques efficaces peuvent être prises pour l'application topique comprenant : 3% en poids de la composition de glycérine, 1,5% de la composition d'alcool benzylique, 1% en poids de la composition de diclofénac sodique, 3% en poids de la composition d'hyaluronate de sodium, ayant un poids moléculaire de 661 600 daltons, 3% en poids de la composition de cire liquide et d'eau stérile dans laquelle le poids total de ladite composition est pratiquement 1569 g, ladite composition est dans une forme dosée appropriée pour l'application topique et ladite composition pharmaceutique comprend une pluralité de quantités dosées dont chacune est dans une quantité dosée dans laquelle l'hyaluronate de sodium est dans une quantité suffisante pour fournir un dosage dépassant 5 mg/cm^2 de la peau ou tissu exposé auquel elle doit être appliquée et dans une forme immédiatement disponible pour transporter le diclofénac sodique par voie percutanée dans l'épiderme de la peau ou tissu exposé au site de la lésion et/ou pathologie de la maladie ou affection dans la peau ou tissu exposé lors de l'application à la peau et/ou tissu exposé pour l'accumulation dans l'épiderme avant passage à partir de là

60. Composition pharmaceutique pour l'application topique à partir de laquelle un nombre substantiel de quantités dosées non toxiques efficaces peuvent être prises pour l'application topique comprenant . 5% en poids de la composition de glycérine, 3% en poids de la composition d'alcool benzylique, 3% en poids de la composition de diclofénac sodique. 2.5% en poids de la composition d'hyaluronate de sodium ayant un poids moléculaire de 661 600 daltons et de l'eau stérile, dans laquelle le poids total de ladite composition est d'environ 3200 g, ladite composition est dans une forme dosée appropriée pour l'application topique et ladite composition pharmaceutique comprend une pluralité de quantités dosées dont chacune est dans une quantité dosée dans laquelle l'hyaluronate de sodium est dans une quantité suffisante pour fournir un dosage dépassant 5 mg/cm^2 de la peau ou tissu exposé auquel elle doit être appliquée et dans une forme immédiatement disponible pour transporter le diclofénac sodique par voie percutanée dans l'épiderme de la peau ou tissu exposé au site de la lésion et/ou pathologie de la maladie ou affection dans la peau ou tissu exposé lors de l'application à la peau et/ou tissu exposé pour l'accumulation dans l'épiderme avant passage à partir de là.

61. Composition pharmaceutique pour l'application topique à partir de laquelle un nombre substantiel de quantités dosées non toxiques efficaces peuvent être prises pour l'application topique comprenant : 20% en poids de la composition de méthoxypolyéthylèneglycol, 1% en poids de la composition d'alcool benzylique, 3% en poids de la composition de diclofénac sodique, 2,5% en poids de la composition d'hyaluronate de sodium ayant un poids moléculaire de 679 000 daltons et de l'eau stérile, dans laquelle le poids total de ladite composition est pratiquement 1597 g, ladite composition est dans une forme dosée appropriée pour l'application topique et ladite composition pharmaceutique comprend une pluralité de quantités dosées dont chacune est dans une quantité dosée dans laquelle l'hyaluronate de sodium est dans une quantité suffisante pour fournir un dosage dépassant 5 mg/cm^2 de la peau ou tissu exposé auquel elle doit être appliquée et dans une forme immédiatement disponible pour transporter le diclofénac sodique par voie percutanée dans l'épiderme de la peau ou tissu exposé au site de la lésion et/ou pathologie de la maladie ou affection dans la peau ou tissu exposé lors de l'application à la peau et/ou tissu exposé pour l'accumulation dans l'épiderme avant passage à partir de là.

62. Composition pharmaceutique pour l'application topique à partir de laquelle un nombre substantiel de quantités dosées non toxiques efficaces peuvent être prises pour l'application topique comprenant : 20% en poids de la composition d'un solubilisant, le méthoxypolyéthylèneglycol, 1% en poids de la composition d'un conservateur, l'alcool benzylique, 3% en poids de la composition de diclofénac sodique, 2,5% en poids de la composition d'hyaluronate de sodium ayant un poids moléculaire de 679 000 daltons, et de l'eau stérile, dans laquelle le poids total de ladite composition est pratiquement 1597 g, ladite composition est dans une forme dosée appropriée pour l'application topique et ladite composition pharmaceutique comprend une pluralité de quantités dosées dont chacune est dans une quantité dosée dans laquelle l'hyaluronate de sodium est dans une quantité suffisante pour fournir un dosage dépassant 5 mg/cm^2 de la peau ou tissu exposé auquel elle doit être appliquée et dans une forme immédiatement disponible pour transporter le diclofénac sodique par voie percutanée dans l'épiderme de la peau ou tissu exposé au site de la lésion et/ou pathologie de la maladie ou affection dans la peau ou tissu exposé lors de l'application à la peau et/ou tissu exposé pour l'accumulation dans l'épiderme avant passage à partir de là.

63. Composition pharmaceutique pour l'application topique à partir de laquelle un nombre substantiel de quantités dosées non toxiques efficaces peuvent être prises pour l'application topique comprenant : 5,5% en poids de la composition de méglumine, 5% en poids de la composition d'ibuprofène, 1% en poids de la composition d'alcool benzylique, 1% en poids de la composition de glycérine, 3% en poids de la composition d'hyaluronate de sodium ayant un poids moléculaire de 661 600 daltons, et de l'eau stérile, dans laquelle le poids total de ladite composition est 227 g, ladite composition est dans une forme dosée appropriée pour l'application topique et ladite composition pharmaceutique comprend une pluralité de quantités dosées dont chacune est dans une quantité dosée dans laquelle l'hyaluronate de sodium est dans une quantité suffisante pour fournir un dosage dépassant 5 mg/cm^2 de la peau ou tissu exposé auquel elle doit être appliquée et dans une forme immédiatement disponible pour transporter le diclofénac sodique par voie percutanée dans l'épiderme de la peau ou tissu exposé au site de la lésion et/ou pathologie de la maladie ou affection dans la peau ou tissu exposé lors de l'application à la peau et/ou tissu exposé pour l'accumulation dans l'épiderme avant passage à partir de là.

64. Composition pharmaceutique pour l'application topique à partir de laquelle un nombre substantiel de quantités dosées non toxiques efficaces peuvent être prises pour l'application topique comprenant : 4% en poids de la composition de méglumine, 2% en poids de la composition de piroxicam, 2,5% en poids de la composition d'hyaluronate de sodium ayant un poids moléculaire de 661 600 daltons. et de l'eau stérile, dans laquelle le poids total de ladite composition est 217 g, ladite composition est dans une forme dosée appropriée pour l'application topique et ladite composition pharmaceutique comprend une pluralité de quantités dosées dont chacune est dans une quantité dosée dans laquelle l'hyaluronate de sodium est dans une quantité suffisante pour fournir un dosage dépassant 5 mg/cm^2 de la peau ou tissu exposé auquel elle doit être appliquée et dans une forme immédiatement disponible pour transporter le diclofénac sodique par voie percutanée dans l'épiderme de la peau ou tissu exposé au site de la lésion et/ou pathologie de la maladie ou affection dans la peau ou tissu exposé lors de l'application à la peau et/ou tissu exposé pour l'accumulation dans l'épiderme avant passage à partir de là.

65. Composition pharmaceutique pour l'application topique à partir de laquelle un nombre substantiel de quantités dosées non toxiques efficaces peuvent être prises pour l'application topique comprenant : une phase huileuse comprenant : 15% en poids de la composition d'une cire liquide, 16% en poids de la composition de cire, 5% en poids de la composition de glycérine et une phase aqueuse comprenant : 5% en poids de la composition de méglumine, 5% de la composition d'ibuprofène, 1,5% en poids de la composition d'hyaluronate de sodium ayant un poids moléculaire de 200 000 daltons, et 0.3% en poids de la composition d'un conservateur. la suttocide A et de

l'eau stérile, dans laquelle le poids total de ladite composition est 3384 g, ladite composition est dans une forme dosée appropriée pour l'application topique et ladite composition pharmaceutique comprend une pluralité de quantités dosées dont chacune est dans une quantité dosée dans laquelle l'hyaluronate de sodium est dans une quantité suffisante pour fournir un dosage dépassant 5 mg/cm^2 de la peau ou tissu exposé auquel elle doit être appliquée et dans une forme immédiatement disponible pour transporter le diclofénac sodique par voie percutanée dans l'épiderme de la peau ou tissu exposé au site de la lésion et/ou pathologie de la maladie ou affection dans la peau ou tissu exposé lors de l'application à la peau et/ou tissu exposé pour l'accumulation dans l'épiderme avant passage à partir de là.

66. Composition pharmaceutique pour l'application topique à partir de laquelle un nombre substantiel de quantités dosées non toxiques efficaces peuvent être prises pour l'application topique comprenant : 3% en poids de la composition de glycérine, 1,5% en poids de la composition d'alcool benzylique, 3% en poids de la composition de cire liquide, 1% en poids de la composition de diclofénac sodique, 3% en poids de la composition d'hyaluronate de sodium ayant un poids moléculaire de 679 000 daltons, et de l'eau stérile, dans laquelle le poids total de ladite composition est 3101 g, ladite composition est dans une forme dosée appropriée pour l'application topique et ladite composition pharmaceutique comprend une pluralité de quantités dosées dont chacune est dans une quantité dosée dans laquelle l'hyaluronate de sodium est dans une quantité suffisante pour fournir un dosage dépassant 5 mg/cm^2 de la peau ou tissu exposé auquel elle doit être appliquée et dans une forme immédiatement disponible pour transporter le diclofénac sodique par voie percutanée dans l'épiderme de la peau ou tissu exposé au site de la lésion et/ou pathologie de la maladie ou affection dans la peau ou tissu exposé lors de l'application à la peau et/ou tissu exposé pour l'accumulation dans l'épiderme avant passage à partir de là.

67. Composition pharmaceutique pour l'application topique à partir de laquelle un nombre substantiel de quantités dosées non toxiques efficaces peuvent être prises pour l'application topique comprenant : 1,5% en poids de la composition d'un conservateur, l'alcool benzylique, 3% en poids de la composition de glycérine, environ 1% en poids de la composition de diclofénac sodique, 3% en poids de la composition de cire liquide, 3% en poids de la composition d'hyaluronate de sodium ayant un poids moléculaire de 661 600 daltons, et de l'eau stérile, dans laquelle le poids total de ladite composition est d'environ 1569 g, ladite composition est dans une forme dosée appropriée pour l'application topique et ladite composition pharmaceutique comprend une pluralité de quantités dosées dont chacune est dans une quantité dosée dans laquelle l'hyaluronate de sodium est dans une quantité suffisante pour fournir un dosage dépassant 5 mg/cm^2 de la peau ou tissu exposé auquel elle doit être appliquée et dans une forme immédiatement disponible pour transporter le diclofénac sodique par voie percutanée dans l'épiderme de la peau ou tissu exposé au site de la lésion et/ou pathologie de la maladie ou affection dans la peau ou tissu exposé lors de l'application à la peau et/ou tissu exposé pour l'accumulation dans l'épiderme avant passage à partir de là.

68. Composition pharmaceutique pour l'application topique à partir de laquelle un nombre substantiel de quantités dosées non toxiques efficaces peuvent être prises pour l'application topique comprenant : une phase huileuse comprenant 15% en poids de la composition d'une cire liquide, 16% en poids d'une cire et 5% en poids de la composition de glycérine, et une phase aqueuse comprenant 5% en poids de la composition de méglumine, 1.5% en poids de la composition d'hyaluronate de sodium ayant un poids moléculaire de 207 000 daltons. 5% en poids de la composition d'ibuprofène et 0.3% en poids de la composition d'un conservateur, le suttocide, et de l'eau stérile, dans laquelle le poids total de ladite composition est 3384 g, ladite composition est dans une forme dosée appropriée pour l'application topique et ladite composition pharmaceutique comprend une pluralité de quantités dosées dont chacune est dans une quantité dosée dans laquelle l'hyaluronate de sodium est dans une quantité suffisante pour fournir un dosage dépassant 5 mg/cm^2 de la peau ou tissu exposé auquel elle doit être appliquée et dans une forme immédiatement disponible pour transporter le diclofénac sodique par voie percutanée dans l'épiderme de la peau ou tissu exposé au site de la lésion et/ou pathologie de la maladie ou affection dans la peau ou tissu exposé lors de l'application à la peau et/ou tissu exposé pour l'accumulation dans l'épiderme avant passage à partir de là.

69. Composition pharmaceutique pour l'application topique à partir de laquelle un nombre substantiel de quantités dosées non toxiques efficaces peuvent être prises pour l'application topique comprenant : 2,5% en poids de la composition d'hyaluronate de sodium ayant un poids moléculaire de 661 600 daltons, 1% en poids de la composition de banamine, et de l'eau stérile, dans laquelle le poids total de ladite composition est 3000 ml, ladite composition est dans une forme dosée appropriée pour l'application topique et ladite composition pharmaceutique comprend une pluralité de quantités dosées dont chacune est dans une quantité dosée dans laquelle l'hyaluronate de sodium est dans une quantité suffisante pour fournir un dosage dépassant 5 mg/cm^2 de la peau ou tissu exposé

auquel elle doit être appliquée et dans une forme immédiatement disponible pour transporter le diclofénac sodique par voie percutanée dans l'épiderme de la peau ou tissu exposé au site de la lésion et/ou pathologie de la maladie ou affection dans la peau ou tissu exposé lors de l'application à la peau et/ou tissu exposé pour l'accumulation dans l'épiderme avant passage à partir de là.

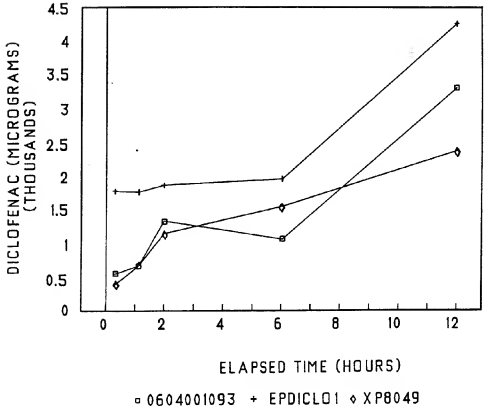

DICLOFENAC (MICROGRAMS)
(THOUSANDS)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
2
4
6
8
10
12
ELAPSED TIME (HOURS)
▫ 0604001093 + EPDICL01 ◇ XP8049

FIG.1.

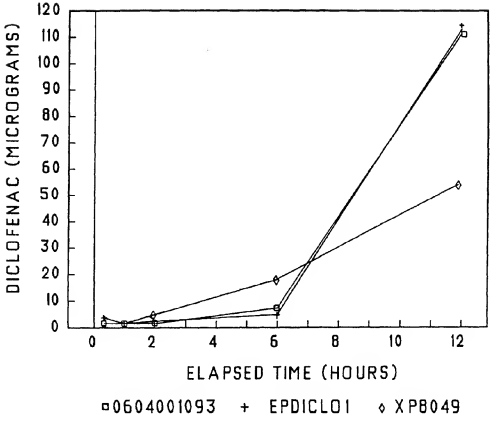

DICLOFENAC (MICROGRAMS)
120
110
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
ELAPSED TIME (HOURS)
▫0604001093 + EPDICLO1 ◇ XP8049

FIG 2'

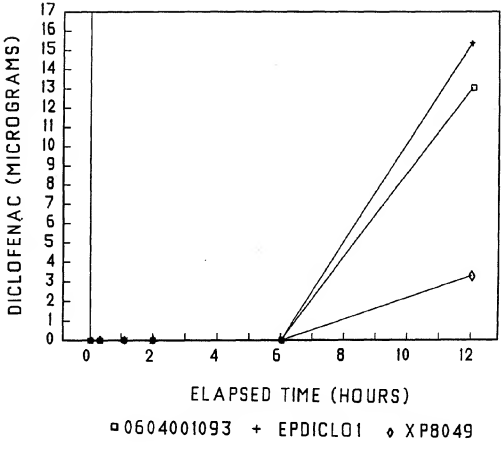

DICLOFENAC (MICROGRAMS)
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
0
2
4
6
8
10
12
ELAPSED TIME (HOURS)
□ 0604001093 + EPDICL01 ◊ XP8049

FIG.3'.

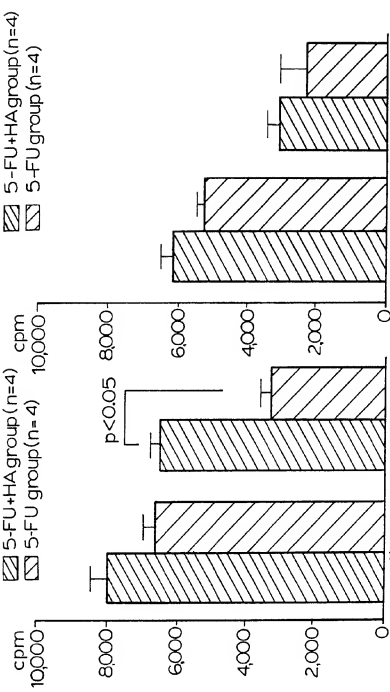

5-FU+HA group (n=4)
5-FU group (n=4)
cpm
10,000
8,000
6,000
4,000
2,000
0
p<0.05
1hr
6hr
5-FU+HA group (n=4)
5-FU group (n=4)
cpm
10,000
8,000
6,000
4,000
2,000
0
1hr
6hr

FIG 4'

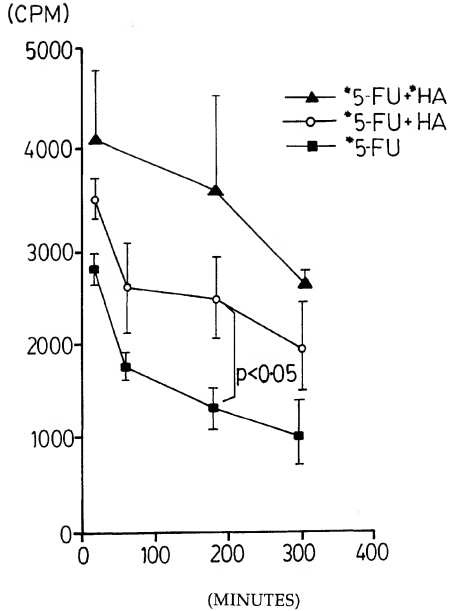
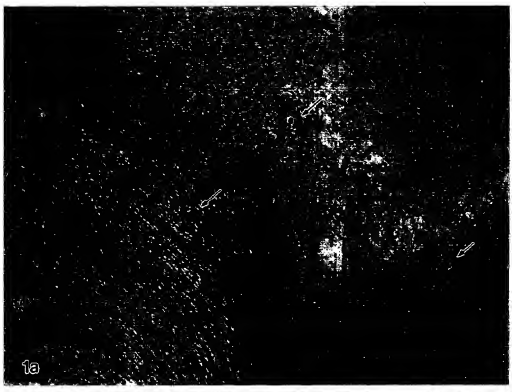
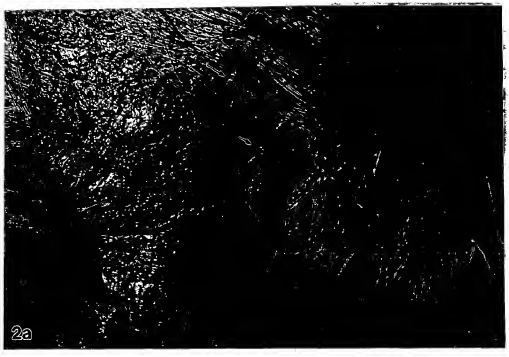
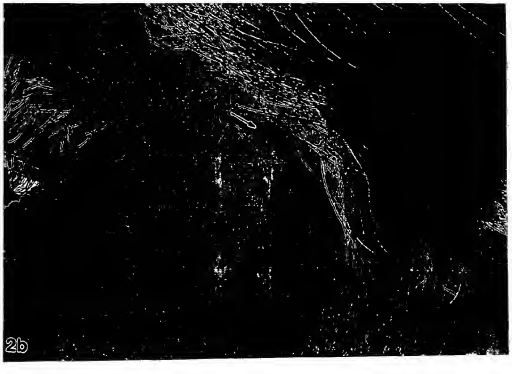

(CPM)
5000
4000
3000
2000
1000
0
0
100
200
300
400
(MINUTES)
*5-FU+*HA
*5-FU+HA
*5-FU
p<0·05

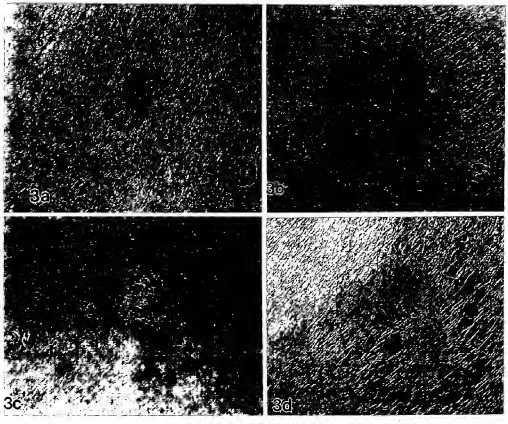
FIG. 5'

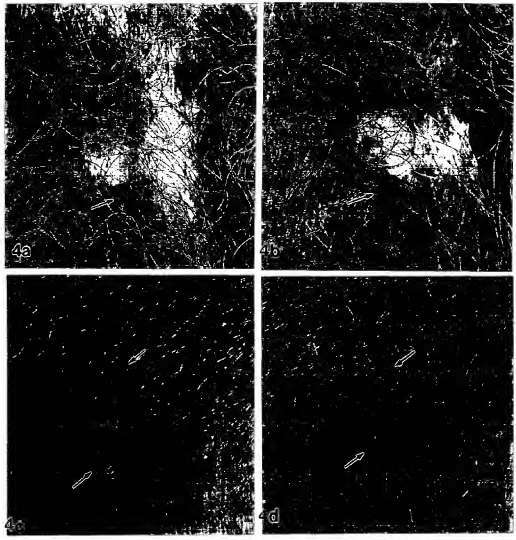

1a

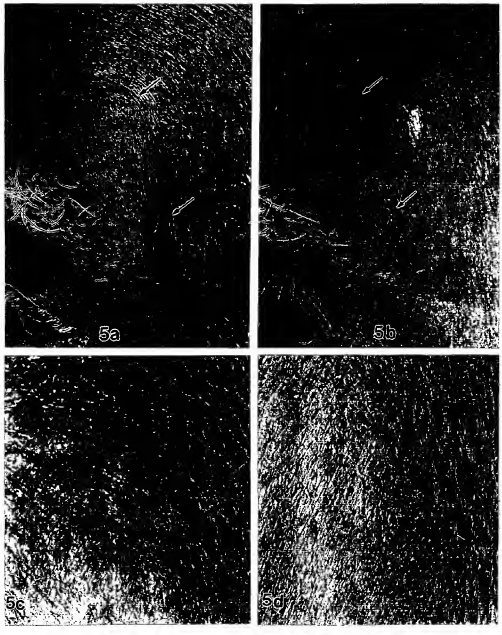

1b


2a


2b


3a
3b
3c
3d

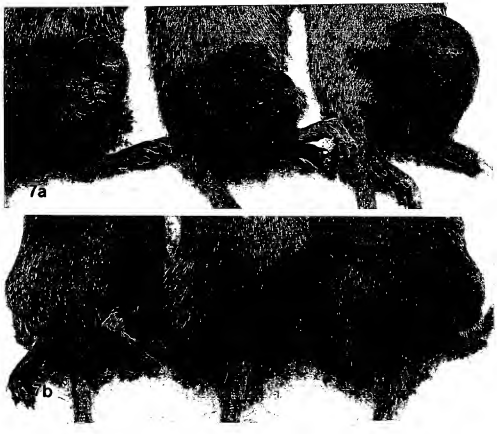

4a
4b
4c
4d


5a
5b
5c
5d


6a


6b


6c


7a
7b